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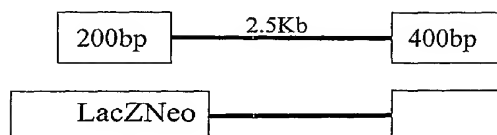
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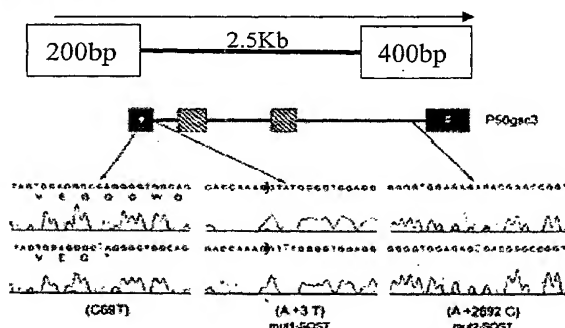
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(54) Title: WISE/SOST NUCLEIC ACID SEQUENCES AND AMINO ACID SEQUENCES

### Wise/Sost



Tooth Overgrowth/ Eye Defects



Bone Overgrowth

(57) Abstract: The present invention relates to nucleic acid sequences and amino acid sequences which influence bone deposition, the Wnt pathway, ocular development, tooth development, and may bind to LRP. The nucleic acid sequence and polypeptides include Wise and Sost as well as a family of molecules which express a cysteine knot polypeptide. Additionally, the present invention relates to various molecular tools derived from the nucleic acids and polypeptides including vectors, transfected host cells, monoclonal antibodies, Fab fragments, and methods for impacting the pathways.

## WISE/SOST NUCLEIC ACID SEQUENCES AND AMINO ACID SEQUENCES

This application is a non-provisional patent application based on U.S. Provisional Patent Application Serial No. 60/388,970, filed June 14, 2002, and a new U.S. non-provisional  
5 application based on Serial No. 60/388,970 filed June 16, 2003.

### FIELD OF INVENTION

The present invention relates to Wise and Sost nucleic acid sequences and related amino acid sequences that can be used to influence bone deposition, the Wnt pathway, tooth development, and ocular development. In particular, the present invention also relates to nucleic  
10 acid sequences and amino acid sequences that optionally regulate or suppress bone deposition. The present invention relates to a family of nucleic acid molecules which expresses a family of amino acid sequences, some of which are characterized by a cysteine knot, such as the Wise and Sost proteins. The present invention also relates to resultant molecular biology tools derived from Wise or Sost, including plasmids, transfected host cells, antibodies, tranfected host  
15 organisms, and knockout organisms. Finally, the present invention relates to the interaction between Wise or Sost and LRP.

### BACKGROUND OF INVENTION

To activate and study the Wnt pathway, a wide range of materials and information has  
20 been used. Various model organisms explained below are used because of differing developmental characteristics associated with the organisms. Because frogs and mice are exemplary of the organisms of study, they are explained in greater detail below. As will be seen,



frogs and mice were used in many of the Examples contained herein. Additionally, various genes and the Wnt pathway are explained.

### **Background of the Frog.**

Frogs, in particular *Xenopus*, are excellent model organisms for testing embryonic development. Two species of *Xenopus* are commonly used for testing, *Xenopus laevis* and *Xenopus tropicalis*. Both *Xenopus* species are natives of Africa. *Xenopus laevis* has been used for many years to investigate the early period of embryonic development. Embryos develop rapidly after fertilization, and a tadpole with a fully functional set of organs forms within a couple of days. Thus, experiments can be conducted on the embryos directly following fertilization. The embryos can develop in a simple saline solution over a few days. The tadpoles are then examined to determine if the experimental intervention had any observable effect. The role of genes in development can be assayed by injecting a tiny amount of any messenger RNA (mRNA) encoding the gene of interest into an early embryo, then once again allowing the embryo to grow into a tadpole.

The *Xenopus* embryo has long served as a major model for the study of embryonic development because of its numerous advantages, including external development, large size, identifiable blastomeres, and its ability to withstand extensive surgical intervention and culture *in vitro*. These advantages enable extensive investigation of the earliest embryonic patterning events. In fact, much of the current understanding of early embryonic development derives from experiments performed in the *Xenopus* embryo.

More particular to the frog, the earliest events of all animal embryos are controlled by mRNAs that are deposited in the egg by the mother. These maternal mRNAs control the embryonic processes that occur prior to the transcription of the embryonic genome. These

processes can best be examined in *Xenopus* because, in these embryos, they occur during an especially long period of time, and because they occur while the embryo is developing externally. Such features have resulted in a detailed cellular and molecular understanding of early patterning events, including a comprehensive view of the role of specific extracellular growth factors, cell surface receptors, and intracellular signaling pathway components. These events include the patterning of the basic body plan, the determination of cell fate, and the early patterning of major organs, including the digestive system, circulatory system, and nervous system. In addition, many of the factors originally identified in *Xenopus* have been subsequently shown to control numerous later developmental events, as well as other critical biological processes, and oncogenesis. Finally, *Xenopus* is a major contributor to understanding cell biological and biochemical processes, including chromosome replication; chromatin, cytoskeleton, and nuclear assembly; cell cycle progression; and, intracellular signaling. Thus, *Xenopus* is ideally suited for studying early embryonic patterning and cell fate determination, later development, and organogenesis, oncogenesis, and cell biological and biochemical processes.

### **Background of A-P Patterning.**

The mechanisms that generate regional differences along the anterior posterior (A-P) axis of the vertebrate nervous system play an important role in pattern formation during development. The classical activation/transformation model proposed by Nieuwkoop suggests that an initial signal induces neural tissue of anterior type and then a second transforming signal differentially acts on it to convert cells to a more posterior character (Nieuwkoop, 1952; Slack and Tannahill, 1992). This transformer or "posteriorizing factor(s)" thus modifies a ground state to generate the full spectrum of neural structures along the A-P axis. However, patterning of the anterior region

is clearly more complicated than a simple default state of neural induction. This is highlighted by the presence of local inductive centers, such as the anterior visceral endoderm and the isthmus, which are essential for anterior neural development. Hence, models for a coordinated mechanism of A-P patterning in the nervous system need to integrate the influence of local signals on rostral brain patterning, with the influence of posteriorizing factors that work more generally on the hindbrain and spinal cord.

Analysis of posteriorizing signals in neural patterning is complicated by the tissue interactions and dynamic morphogenetic movements which occur during gastrulation. *Xenopus* animal caps provide a simplified system for studying patterning events separately from morphogenetic movements. Animal caps alone form epidermis in culture, but when treated with antagonists of Bone Morphogenic Protein (BMP) signaling, such as Noggin, Chordin, Follistatin, or truncated BMP receptors, they adopt an anterior neural fate. Using these molecules as neural inducers, experimental studies in animal caps have provided evidence that fibroblast growth factor (FGF), retinoic acid (RA), and Wnt (Wingless and iNT-1) signaling pathways influence A-P patterning by inducing posterior characters. Wnt is also known as the canonical Wnt pathway and the Wnt planar polarity pathway. Thus, *Xenopus* embryo assays and experiments in other vertebrates provide more evidence that RA, FGF, and Wnt pathways influence A-P patterning. It is desired to better understand the relative roles of these biochemical cascades, the degree to which they are used at any particular axial level, and how they are integrated in organizing normal A-P patterning.

Mesoderm plays an important early role in A-P patterning of neural tissue. Mesoderm is the middle layer of embryonic cells between the ectoderm and endoderm in triploblastic animals, and forms muscle, connective tissue, blood, lymphoid tissue, the linings of all the body cavities,

the serosa of the viscera, the mesenteries, and the epithelia of the blood vessels, lymphatics, kidney, ureter, gonads, genital ducts, and suprarenal cortex. Experiments in *Xenopus* have shown that planar signals within the neuroectoderm and vertical signals from the underlying mesoderm work in concert to control regional identity of the nervous system. While early A-P  
5 specification of the nervous system occurs during gastrulation, it is not irreversibly committed to a particular identity. Grafting experiments in several species reveal plasticity in regional character and show that mesoderm is still playing a role at later stages. For example, analysis of the Hoxb4 gene has shown that its expression pattern is established through interactive signaling between the neural tube and the surrounding mesoderm. Furthermore, somites and paraxial  
10 mesoderm are sufficient to re-program Hox expression in the neural tube to a more posterior character when grafted ectopically. The ability of mesoderm to regulate regional character from early gastrula stages and to program motor neuron sub-type identities further emphasizes the importance of mesoderm and its signaling in patterning the developing nervous system.

The study of A-P patterning and focus on the mesoderm is of particular importance in the  
15 present invention because such patterning impacts bone development in an embryo. Pathways which control A-P patterning often impact bone development.

As such, it is desired to better understand the process of posteriorization. The identification of new factors that can modulate existing pathways, such as Wnts, FGF, and RA, or which represent novel signaling inputs will be beneficial to understanding how A-P patterning  
20 is coordinated. In particular, it is desired to understand how the Wnt pathway is activated and controlled. *Xenopus* has been used to study A-P patterning, that, in turn, is apparently impacted by the Wnt pathway. *Xenopus* can also be used to study activators or inhibitors of the Wnt pathway.

### **Background of Mouse Model.**

Mice are also excellent model organisms for testing embryonic development. Mice and humans possess similar genes, mice show many clinical symptoms of human disease, and powerful techniques are available for genetic alterations of the mouse genome. All of these factors make mice excellent experimental models for testing new therapies. Mice share many fundamental biological processes with humans therefore, mice are considered to be one of the most significant laboratory models for human disease and genetic mutations. Research regarding human biological processes and genetic diseases can be greatly enhanced by studying the mouse model for similar biological processes and diseases.

Mice have been a preferred experimental model for a number of years due to their small size, short life span, and the female's ability to produce a litter within two months after her birth. These factors allow researchers to follow a given disease process from beginning to end within a short time frame. For these various reasons, mouse models are preferred for testing new drug therapies, designing novel therapies, and studying genetic diseases potentially also affecting humans.

Genes can be inserted into a fertilized mouse egg by several methods including physical injection. The gene is first attached to a promoter and then is injected into the fertilized egg. The fertilized egg is implanted into a female mouse and the embryo is allowed to develop to a specified given stage for study. Once embryos reach the desired stage of development, they can be harvested and tested to determine experimental results. Alternatively, embryos can be allowed to develop into full-term pups prior to being harvested to determine the results of the experiment.

Because mice are phylogenetically closely related to humans with regards to biological processes and diseases, and because of the rapidity of mouse embryological development, they are considered to be an excellent animal model for the study of human development, biological processes, and disease.

## 5            **Background of Wnt.**

Wnt proteins form a family of highly conserved secreted signaling molecules that regulate cell-to-cell interactions during embryogenesis. Wnt genes and Wnt signaling are also implicated in aberrant cancer cell regulation. Insights into the mechanisms of Wnt action have emerged from several systems: genetics in *Drosophila* and *Caenorhabditis elegans* (*C. elegans*);  
10 and, biochemistry in cell culture and ectopic gene expression in *Xenopus* embryos. Many Wnt genes in the mouse have been mutated, leading to very specific developmental defects. As currently understood, Wnt proteins bind to receptors of the Frizzled family on the cell surface. Through several cytoplasmic relay components, the signal is transduced to  $\beta$ -catenin, which then enters the nucleus and forms a complex with TCF or LEF to activate transcription of Wnt target  
15 genes. The extracellular Wnt ligand binds the transmembrane receptor Frizzled (Fz), which activates the cytoplasmic phosphoprotein Dishevelled (Dsh). Activated Dsh inhibits GSK3  $\beta$ -mediated degradation of  $\beta$ -catenin.  $\beta$ -catenin protein, therefore, accumulates and, in association with transcription factors (TCF-3, TCF-4, LEF), regulates gene transcription in the cell nucleus.

Wnt-proteins, secreted glycoproteins, serve as important signaling molecules during  
20 development of invertebrates and vertebrates. They have been shown to play crucial roles in such diverse processes as cancer, organogenesis, and pattern formation. To date, 19 Wnt genes have been isolated in higher vertebrates, 7 have been found in the genome of *Drosophila*, and 5 in the *C. elegans* genome. Wnt genes are defined by their sequence similarity to the founding

members, Wnt-1 in the mouse (originally called iNT-1) and wingless (Wg) in *Drosophila*. The genetic analysis of the Wg signaling pathway in *Drosophila* has led to the identification of many downstream components, which have been shown to be functionally conserved in other organisms. Wg/Wnt-proteins are thought to signal through seven-transmembrane receptors encoded by the Frizzled (Fz) gene family to regulate the stability of an effector protein known as armadillo (Arm) in flies or  $\beta$ -catenin ( $\beta$ -cat) in vertebrates, which eventually leads to the activation of target genes through a complex of Arm/ $\beta$ -cat, with DNA-binding transcription factors of the TCF/LEF family. This pathway is referred to as the canonical Wnt-pathway.

In recent years, evidence has been provided that Wnt signaling in the chick is involved in a variety of processes associated with skeletogenesis, such as chondrogenesis and joint development. Previously, it has been shown that there are at least three Wnt genes, Wnt-4, Wnt-5a, and Wnt-5b, as well as components of the canonical Wnt signaling pathway, expressed in chondrogenic regions, and that there is a fourth Wnt gene, Wnt-14, which is expressed early in the joint forming region (Fig. 1D). Wnt-4 is also expressed in regions of the joint, however, its expression is restricted to cells in the periphery of the joint interzone (Fig. 1C). Wnt-5a expression is restricted to cells in a region of the perichondrium which will develop into the periosteum (Fig. 1A), while the closely related Wnt-5b gene is expressed in a sub-population of prehypertrophic chondrocytes, as well as cells of the outer layer of the perichondrium (Fig. 1B).

Much of what is known about the functional role of Wnt signaling in early vertebrate development comes from experiments with *Xenopus*. Maternally encoded components of the canonical Wnt signaling pathway function to establish the endogenous dorsal axis. The sperm fertilizing the egg triggers cortical rotation. Vesicles are moved towards the future dorsal side. A dorsal determinant, which is likely to be Dishevelled, is transported with these vesicles.

Dishevelled accumulates on the dorsal side and inhibits GSK3.  $\beta$ -catenin can therefore accumulate on the dorsal side and, together with XTcf-3, induce the expression of siamois, which regulates down-stream dorsal development.

As such, the Wnt signaling system is one of only a limited number of signaling systems used during embryonic development to pattern the ultimate resultant morphological physical body construction plan. Clearly, Wnt signaling is triggered at several discrete time points during development, both at different developmental stages and within different tissues (*see* Table below).

TABLE 1

Gene	Expression	Function
XWnt-1	anterior neural	mid-/hindbrain boundary
XWnt-2 (=XWnt-2B)	neural and heart	not known
XWnt-3-A	posterior neural	neural anteroposterior patterning
XWnt-4	neural, kidney (pronephros)	kidney morphogenesis
XWnt-5A	ectoderm	not known
XWnt-8	ventral mesoderm	mesodermal patterning
XWnt-8b	forebrain	not known
XWnt-11	dorsal marginal zone	gastrulation movements

Early *Xenopus* development provides an excellent model system for studying the general questions of tissue-specific response to Wnt signaling. Before the onset of zygotic transcription at the Mid-Blastula Transition (MBT) phase, the Wnt pathway functions to establish the dorsal body axis. Only an hour or two later, after MBT, XWnt-8 functions to promote ventral and lateral mesoderm. These strict stage-specific responses to Wnt signaling could conceivably be induced by differential use of the canonical and alternative Wnt signal transduction pathways.

It is further known to those of skill in the art that Wnt genes are active in osteoblast cells. Wnt regulates bone deposition in embryos and in mature individuals. It has been found that Wnt signals impact the dorsal-ventral pattern in early *Xenopus* embryo. In late embryos, Wnt causes



anterior-posterior patterning of the neural tissue, neural crest formation, and organogenesis. As such, it is desired to have compositions and methods for controlling Wnt signaling. Such compositions and methods would have impact on embryonic developmental processes such as anterior-posterior patterning and on bone deposition.

5           **Background of Sost.**

Sost is believed to be a Bone Morphogenic Protein (BMP) antagonist. Mutations in the human Sost gene on human chromosome 17 can result in sclerosteosis, which is an autosomal recessive sclerosing bone dysplasia characterized by progressive skeletal overgrowth. A high incidence of the bone dysplasia disorder, occurring as a result of a founder effect in affected  
10 individuals has been reported in the Afrikaner population of South Africa, where a majority of individuals are affected by the disorder. Homozygosity mapping in Afrikaner families, along with analysis of historical recombinants, localized sclerosteosis to an interval of ~ 2 cm. between the loci D17S1787 and D17S930 on chromosome 17q12-q21. Affected Afrikaners carry a nonsense mutation near the amino terminus of the encoded protein, whereas an unrelated  
15 affected person of Senegalese origin carries a splicing mutation within the single intron of the gene. The Sost gene encodes a protein that shares structural and functional similarity with a class of cysteine knot-containing factors, including dan, cerberus, gremlin, and caronte. The specific and progressive effect on bone formation observed in individuals affected with sclerosteosis suggests that the Sost gene encodes a regulator of bone homeostasis.

20           As such, evidence is provided herein that the deficiency of the Sost gene product, a novel secreted protein expressed in osteoblasts, leads to the increased bone density in sclerosteosis. The two nonsense mutations, and the splice site mutation, are loss-of-function mutations. Previously, the precise function and working of Sost was believed unknown, an inhibitory effect

on bone formation can be proposed since pathophysiological analysis indicated that sclerosteosis is primarily a disorder of increased formation of normal bone. While it is known that Sost impacts bone formation, it is desired herein to better delineate the mechanism of action and pathway of Sost's bone deposition activity. Previously, it has been hypothesized that Sost  
5 affected BMP rather than the Wnt pathway. Previous to our described invention herein, it was not known that Sost reacted with Wnt pathway elements. The Sost-Wnt pathway interaction can be alternatively direct or indirect in nature.

### **Background of LRP6.**

LRP genes encode the low-density lipoprotein (LDL)-receptor-related proteins, LRP5  
10 and LRP6. Human LRP5 and LRP6 share 71% amino-acid identity, and together with Arrow, form a distinct subgroup of the LRP family. Arrow, LRP5, and LRP6 each contain an extracellular domain with epidermal growth factor (EGF) repeats and low-density lipoprotein receptor (LDLR) repeats, followed by a transmembrane region and a cytoplasmic domain lacking recognizable catalytic motifs. An LRP6 mutation in mice results in pleiotropic defects  
15 recapitulating some, but not all, of the Wnt mutant phenotype. LRP5/LRP6 involvement in Wnt signaling and LRP function in Wnt-induced axis *Xenopus* embryos have been previously studied.

LRPs and Arrow in *Drosophila* are long single-pass transmembrane proteins. These proteins are of interest because they interact with and affect Wnt signaling. Arrow is genetically required for Wingless (Wg) signaling (Wehril, 2000) and mouse LRP mutations are similar in  
20 phenotype to Wnt mutants (Pinson, 2000). In *Xenopus*, over-expression of LRP can activate Wnt signaling (Tamai, 2000). There is evidence that Wnts can bind directly to the extra-cellular domain of LRP and form a ternary complex with the Frizzled receptor (Tamai, 2000). Also, the

cytoplasmic domain of LRP can interact with Axin (Mao, 2001). Thus, LRP/Arrow appear to be important to understanding Wnt.

As stated, the Frizzled (Fz) family of serpentine receptors function as Wnt receptors, but how Fz proteins transduce signaling is not understood. In *Drosophila*, Arrow phenocopies the Wingless (DWnt-1) phenotype, and encodes a transmembrane protein that is homologous to two members of the mammalian low-density lipoprotein receptor (LDLR)-related protein (LRP) family, LRP5 and LRP6. It is reported that LRP6 functions as a co-receptor for Wnt signal transduction. In *Xenopus* embryos, LRP6 activated Wnt-Fz signaling, and induced Wnt responsive genes, dorsal axis duplication, and neural crest formation. An LRP6 mutant lacking the carboxyl intracellular domain blocked signaling by Wnt or Wnt-Fz, but not by Dishevelled or  $\beta$ -catenin, and inhibited neural crest development. The extracellular domain of LRP6 bound Wnt-1 and associated with Fz in a Wnt-dependent manner. This indicates that LRP6 is likely to be a component of the Wnt receptor complex.

Further, Wnt/ $\beta$ -catenin signaling induces dorsal axis formation through activation of immediate, early responsive genes, including nodal-related 3 (Xnr3) and Siamois (Sia). It has been shown that in two developmental processes dependent on the Wnt pathway in *Xenopus* -- secondary axis and neural crest formation -- LRP6 activates, but a dominant-negative LRP6 inhibits, Wnt signaling, providing compelling evidence that LRP6 is critical in Wnt signal transduction. LRP6 functions upstream of Dsh in Wnt-responding cells, synergizes with either Wnt or Fz, and importantly, is able to bind Wnt-1 and to associate with Fz in a Wnt-dependent manner. The simplest interpretation of these findings is that LRP6 is a component of the Wnt-Fz receptor complex.

Genetic studies of Arrow in *Drosophila* and LRP6 in mice strongly support this hypothesis. Data also indicates the possibility that Wnt-induced formation of the Fz-LRP6 complex assembles LRP6, Fz and their associated proteins, thereby initiating cytoplasmic signaling. Consistent with this notion, Wnt signal transduction requires intracellular regions of both Fz and LRP6, which harbor candidate protein-protein interaction motifs. Notably, Arrow does not exhibit Fz planar polarity phenotype, implying that Arrow-LRP6 may specify Wnt-Fz signaling towards the  $\beta$ -catenin pathway. How Fz, LRP6, and proteoglycan molecules, such as Dally, interact to mediate Wnt recognition/specificity, and signal transduction remains to be elucidated. Thus, it is understood that LRP interacts with Wnt. The present invention is designed and characterized to control LRP binding to Wnt and Fz, and, more particularly, to control LRP upstream.

#### **Background of LRP5.**

In humans, low peak bone mass is a recognized significant risk factor for osteoporosis. It has been reported that LRP5, encoding the LDLR-related protein 5, affects bone mass accrual during growth. Mutations in LRP5 cause the autosomal recessive disorder osteoporosis-pseudoglioma syndrome (OPPG). OPPG is an autosomal recessive disease, characterized by severe osteoporosis due to decreased bone formation and pseudoglioma resulting from failed regression of primary vitreal vasculature. Y. Gong, et al. (2001). Gain of gene function leads to high bone mass (HBM) phenotype as an autosomal dominant trait, whereas loss of function leads to osteoporosis.

It has been found that OPPG carriers have reduced bone mass when compared to age- and gender-matched controls. LRP5 expression by osteoblasts *in situ* has been demonstrated and LRP-5 has been shown to reduce bone thickness in mouse calvarial explant cultures. These data

indicate that Wnt-mediated signaling via LRP5 affects bone accrual during growth and is important for the establishment of peak bone mass.

In mice, it has been found that LRP5 participates in bone formation and bone mass. Null mutation of LRP5 causes post-natal bone loss, resulting from decreased bone formation and osteoblast proliferation, independent of Runx2. M. Kato, et al. (2002). In contrast, transgenic mice expressing LRP5 with the HBM mutation G171V exhibit increased bone formation and bone mass, without skeletal developmental abnormalities. F. Bex, et al. (2002).

LRP5 appears to interact with the Wnt pathway since LRP5 with the HBM mutation prevents inhibition of Wnt signaling by Dkkopf-1. L. M. Boyden (2002); A. M. Zorn (2001).

There is murine hybridization and microarray evidence that indicates Wnt signaling is involved in bone fracture repair. M. Hadjiargyrou (2002). Six additional mutations in LRP5, located in the amino-terminal domain near G171, have been identified. These mutations cause increased bone density, particularly in cortical bone. L. Van Wesenbeeck (2003).

#### **Background of $\beta$ -catenin.**

$\beta$ -catenin reports demonstrate its accumulation opposite the sperm entry point by the end of the first cell cycle.  $\beta$ -catenin continues to accumulate in dorsal (*i.e.*, opposite the sperm entry point) but not ventral cytoplasm through the early cleavage stages. By the 16- to 32-cell stages, it accumulates in dorsal but not ventral nuclei. Remarkably, the pattern of dorsal accumulation of  $\beta$ -catenin closely parallels the ability of transplanted dorsal cells to induce an axis when implanted into host embryos. Thus,  $\beta$ -catenin is the first signaling molecule to show a dorso-ventral polarity in the early embryo. Combined with the loss-of-function data from Heasman et al., it is now clear that when fertilization elicits a cortical rotation, and displacement of material

and organelles to the future dorsal side, it leads to a dorso-ventral asymmetry in  $\beta$ -catenin, which is required for axis formation.

Brannon et al. show that the HMG Box factor XTCF-3 directly binds the siamois promoter. In the absence of  $\beta$ -catenin, XTCF-3 inhibits gene expression. However, on the dorsal side of the embryo,  $\beta$ -catenin binds the XTCF-3, and, thus, activates the gene. This is notable because siamois is a homeobox gene likely playing a major role in specifying formation of Spemann's Organizer. Therefore, a dorso-ventral difference in  $\beta$ -catenin forms within an hour or two of fertilization, directly regulating a key homeobox gene in the blastula, thus contributing to formation of Spemann's Organizer on the dorsal side of the gastrula.

$\beta$ -catenin not only impacts development, but it influences bone development in adults. Regulation of osteoblasts results from accumulation of  $\beta$ -catenin in the cell. It is desired to have methods and compositions for controlling bone deposition. It is known that the Wnt pathway controls accumulation of  $\beta$ -catenin, which regulates osteoblast expression. It is desired to control and inhibit osteoblast regulation by preventing Wnt pathway activation. For this reason, the present invention includes nucleic acid molecules and amino acid sequences for controlling Wnt.

#### SUMMARY OF INVENTION

The present invention relates to Wise nucleic acid sequences and amino acid sequences, Sost nucleic acid sequences and amino acid sequences, and LRP nucleic acid sequences and amino acid sequences. Additionally, the present invention relates to control over the influencing of bone deposition, ocular development, tooth development, and the Wnt pathway using the above nucleic acid sequences and amino sequences. Additionally, the present invention relates to molecular tools developed from the nucleic acids and polypeptides including

vectors, transfected host cells, transfected organisms, knockout organisms, antibodies, hybridomas cells, Fab fragments, and homologous nucleic acid sequences and polypeptides. Mutants of the Wise, Sost, and LRP nucleic acid sequences and polypeptides are contemplated herein and are used to influence the pathways. The Wise and Sost nucleic acid sequences are generally about 70% homologous. Related to this are cysteine knot polypeptides which bind to LRPs as well as a variety of polypeptides. There is a family of nucleic acid sequences and polypeptides expressed therefrom, which are related to the Wise and Sost sequences. The host cells that can be treated with the mutants of the present invention include insects, amphibian, and mammalian cells.

Nucleic acid sequences, and the resultant polypeptides, are members of a family of isolated nucleic acid molecules which influence one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development is contemplated herein. The family includes a variety of nucleic acid molecules including NDP, DAN, Caronte, PDGF, Wise, Sost, Cereberus, Gremlin, CTGF, Soggy, DKK1, Cyr61, DKK2, DKK3, DKK4, NOV, Mucin, Slit, OOH, Wisp, and CCN. Related to this are the LRP family of molecules which also influence these various pathways. In particular, LRP 1, 2, 5, and 6. As such, the family that expresses a cysteine knot polypeptide binds to one of the LRPs. The various nucleic acids are specifically listed in the Sequence ID listing included herewith. Related to this are degenerate variants of the nucleic acid molecules. As mentioned, the family of nucleic acid molecules typically expresses a polypeptide that includes a cysteine knot protein, with the cysteine knot protein including eight cysteine residues. However, variations of the cysteine knot protein are available for use. As such, any nucleic acid sequence which impacts the previously mentioned pathways and expresses a cysteine knot protein is believed related to the present family of

nucleic acid sequences. It is known that Exon 2 of the Wise nucleic acid sequence (SEQ. ID. NO. 128) expresses a desired cysteine knot protein. As such, oligonucleotide fragments which are 70% homologous to Wise Exon 2 are believed to be potentially related to the present family of nucleic acid molecules.

5           Mutant versions of the above nucleic acid molecules can result in increased bone deposition, as well as tooth development and ocular development. Additionally, the mutants will influence with Wnt pathway activation. As such, mutant versions of the nucleic acid molecules of the present invention are known to impact the mentioned pathways in a variety of ways. The present invention resultingly relates to any mutant version of the listed nucleic acid sequences.

10   The mutants can be generated via point, frame shift, deletion, or loss of function mutations. Loss of function mutations can be achieved by placing a stop codon near the beginning of the selected nucleic acid sequences, which would include before or after the start of the sequence. For example, a stop codon can be placed just after the start of Exon 1 of the Wise nucleic acid sequence. During translation the stop codon will prevent translation of the Wise Exons and

15   therefore the polypeptide will not be expressed. Other available mutants include antisense RNAs, morpholinos, antisense oligonucleotides, mRNAs translated from the selected nucleic acid sequences, and RNAi complementary to the nucleic acids sequences.

As discussed herein, nucleic acid sequences and nucleic acid molecules will be used interchangeably. The isolated nucleic acid sequences include gDNAs, cDNAs, and a

20   variety of other nucleic acid sequence fragments. It is contemplated that any of a variety of nucleic acid sequences can be used herein including genes, mRNA, cDNA, gDNA, tRNA, oligonucleotides, polynucleotides, and nucleic acid sequence fragments. As such, any nucleic acid sequence which expresses a polypeptide that influences either tooth development, Wnt



pathway activation, bone deposition, or ocular development is contemplated as part of the present invention, as well as mutant versions thereof. The nucleic acid sequences will include genes which are any hereditary unit that has an affect on the phenotype of an organism and can be transcribed into mRNAs which result in polypeptides, as well as rRNAs or tRNA molecules and regulatory genes. Also, alleles and mutant alleles are part of the definition of a gene as used herein.

Probes which hybridize to either mutant nucleic acid sequences or the non-mutant nucleic acid sequences are part of the present invention. The probes will include any of a variety of labels and can be either cDNA or RNA probes. The probes can be used to form a kit or similar tool for use in detecting the presence or absence of a particular Wise, Sost, or LRP nucleic acid or polypeptide.

Vectors are formed from both the isolated nucleic acid sequences and the mutant versions of the isolated nucleic acid sequences. The vectors include expression, cloning, and viral vectors. Other available vectors include fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors. Also, prokaryotic and eukaryotic vectors may be used. Specific prokaryotic vectors that may be used in the present invention include pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT. Specific eukaryotic vectors that may be used herein include pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis. As mentioned, a variety of promoters may be used

with the vector, as well as any of a variety of selectable markers. Available markers include antibiotic resistance genes, a tRNA gene, auxotrophic genes, toxic genes, phenotypic markers, colorimetric markers, antisense oligonucleotides, restriction endonuclease, enzyme cleavage sites, protein binding sites, and immunoglobulin binding sites. Specific selectable markers  
5 available include LacZ, neo, Fc, DIG, Myc, and FLAG.

Any of a variety of host cells, including prokaryotic and eukaryotic cells, can be transfected with the vectors previously mentioned. Prokaryotic host cells include Gram-negative and Gram-positive bacteria may be transfected with any of the variety of the vectors previously mentioned. Available bacteria include Escherichia, Salmonella, Proteus,  
10 Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas. A preferred Gram-negative bacterium is Escherichia coli. Eukaryotic vectors can be used to transfect eukaryotic host cells including yeast, plant, fish, mammalian, human, mouse, frog, or insect cells. Specific host cells that can be transfected include ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, chondrocytes, and human or mammalian bone marrow  
15 stroma. As such, the present invention includes host cells transfected with any of the previously mentioned vectors.

It is specifically contemplated that mutant Wise nucleic acid sequences can be used. The mutant Wise nucleic acid sequences will be mutated versions of SEQ. ID. NO. 1-5, 126-128, 109, 96, and 97, as well as complementary mutant sequences thereof. Additionally,  
20 degenerate variants of these sequences may also be used. Plasmids can be formed from these mutant Wise nucleic acid sequences, as well as transfected host cells. Additionally, mutant organisms can be formed from the mutant Wise nucleic acid sequences, including Wise mutant mice. Sost and LRP can also be mutantized and various related constructs can be formed

therefrom. Specific mutants to either Wise, Sost, or LRP can be developed related to SEQ. ID. NO. 1-44, 96-103, 108, 110-113 and 126-128 listed herein.

Amino acid sequences which influence at least one of the following, tooth development, Wnt pathway activation, bone deposition, or ocular development are part of the present invention. Available amino acid sequences include those polypeptides or proteins expressed from the previously discussed nucleic acid molecules. In particular, Wise, Sost, and LRP polypeptides and amino acid sequences can be used herewith. Specifically available amino acid sequences include those listed in the SEQ. ID. NO. 45-95, 104-107, 109, 114-125. Isolated polypeptides that have a cysteine knot formed from eight cysteine knot residues which impact the previously listed pathways are included herewith. Finally, amino acid sequences which are 70% homologous to Exon 2 polypeptides of Wise may be used herewith. When used herein amino acid sequences include any of a variety of polypeptide and protein molecules.

Antibodies which bind to at least one of the previously mentioned amino acid sequences are used herewith. The antibodies include monoclonal, polyclonal, recombinant, and antibody fragments. Any of a variety of antibodies may be used that bind to either Wise, Sost, or LRP 1, 2, 5, or 6. The antibodies are designed to either bind to the selected polypeptide and prevent it from binding to its normal antigen. Conversely, the antibodies can be designed such that they attack and destroy the chosen or selected polypeptides. For example, it is preferred to bind either Wise or Sost with Wise or Sost antibody, respectively, whereby Wise or Sost is prevented from binding to LRP 5 or 6. As such, it is desired to have antibodies that specifically bind Wise, Sost, or LRP. Related to the antibodies are Fab fragments which function the same way as the chosen antibodies. These anti-peptide antibodies will prevent binding by the selected amino acid sequence to an LRP for example. The antibodies can be directed to both mutant and

non-mutant versions of polypeptides expressed from the mutant or non-mutant versions of the nucleic acid sequences.

Hybridomas can be formed which are used to produce the desired antibodies. As such any of a variety of cells can be used to produce both the polypeptides as well as the antibodies.

It is known that both Wise and Sost polypeptides bind to LRP 5 or 6 polypeptides. As such, the present invention relates to a protein molecule formed from a Wise polypeptide bound to an LRP polypeptide. Additionally, the present invention relates to a Sost polypeptide bound to an LRP polypeptide.

Use of the isolated nucleic acid sequences or polypeptides can specifically result in increased bone deposition, both *in vivo* and *in vitro*. As such a variety of methods can be practiced which are designed to increase the bone deposition either in a selected cell or a selected host organism. One particular method includes isolating a nucleic acid sequence which can be either Wise, Sost, or LRP. The nucleic acid sequence then is used to form a cassette which includes a stop codon at the beginning of the nucleic acid sequence. Preferably, the cassette will include a marker and a promoter. The selected nucleic acid sequence can be either a mutant or a non-mutant nucleic acid sequence, with the sequence selected dependent upon the desired outcome. The cassette is then used to form a plasmid whereby any of a variety of plasmids, as previously mentioned, may be used. Once the plasmid is formed it is used to transfect a host cell. Any of a variety of methods can be used to transfect a host cell including microinjection. The available host cell will include a variety of prokaryotic and eukaryotic cells. Among the available cells are embryonic stem cells, blastomeres, and a variety of other stem cells. Once the host cell is transfected the stop codon can be activated to cause a loss of function mutation which

results in a phenotypic change. Among the phenotypic changes are increased bone deposition.

The transfected host cells can also be used to transfect a host cell organism such as a mouse. The cells are injected into an embryo with the embryo then allowed to develop or mature. Host cells include insect, amphibian, and non-human mammal. Human cells can also be treated *in vitro*.

5 Specific delivery of the nucleic acid sequence into the host cell can be accomplished via microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation. Desired host cells include osteoblasts, osteoclasts, and chondrocytes. Besides attaching stop codons to the nucleic acid sequence in the plasmid, other mutantized versions may be used. In particular, an alternative to the stop codon are point mutations, frame shift mutations, and other  
10 mutations may be used to preclude accurate translation of the polypeptide. This will resultingly achieve the same effect as a loss of function mutation. In particular, antisense RNA vectors may be used in the alternative.

Bone deposition can also be increased as an alternative method. A nucleic acid sequence can be selected, including Wise, Sost, or LRP. A nucleic acid sequence is then used to  
15 form a plasmid vector whereby the vector is used to transfect the host cell. The host cell will express the nucleic acid sequence to produce a polypeptide. Once a sufficient amount of polypeptide is produced it can be harvested for use in immunizing a host organism. Available host organisms include mice, rats, goats, rabbits, and any of a variety of other organisms used to produce polypeptides. The immunized host organism will produce antibodies to the polypeptide  
20 that was used to immunize the host.. After a period of time the antibodies may be isolated and separated from the host. The antibodies can be used as is or can be further treated to produce Fab fragments or related small molecules. Regardless of the selected form of the antibody it can be combined with a carrier. Any of a variety of carriers are available for use including liposomes.

The carrier antibody combination is used to transfect a host cell. This can be done either *in vitro* or *in vivo*. The antibody will bind to the selected target polypeptide and prevent activation of a selected pathway. This process can also be used in association with the Wnt pathway, tooth development or ocular development.

- 5 Any of a variety of kits may be formed both to the polypeptides or the nucleic acid sequences of the previously mentioned constituents. The kits can be used to detect the presence of a particular nucleic acid sequence or polypeptide or the absence of such composition.

#### BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the isolation of Wise by *Xenopus* animal cap screening;

- 10 Fig. 1A shows an illustration of the screening procedure;

Fig. 1B shows the RT-PCR gel electrophoresis results of the first round of screening;

Fig. 1C shows the RT-PCR analysis of injections using RNA from the isolated Wise clone;

Fig. 2 shows Wise as a conserved secreted protein;

- 15 Fig. 2A shows the alignment of the predicted amino acid sequence of Zebrafish, *Xenopus*, chick, mouse, and human Wise proteins. Shaded boxes represent identical amino acids between species; asterisks indicate residues conserved in *Drosophila* Slit, and dots identify residues conserved in Cefl0. Circles mark conserved cysteine residues. The arrowhead delineates the site of signal peptide cleavage predicted in the chick clone;

- 20 Fig. 2B is a diagram showing alignment of conserved amino acids between Wise, Slit, and Cefl0 (a CCN family member). Filled ovals and red lines indicate cysteine residues in the Slit homology domain conserved in the CT domain of CCN family members but not in Wise or

Slit. Dotted lines show other conserved amino acids. Shaded boxes in Wise indicate three blocks  $\Delta 1$ ,  $\Delta 2$ ,  $\Delta 3$  deleted separately for functional analysis;

Fig. 2C shows Western blot detecting HA-tagged Wise protein secreted into the medium following RNA injection into oocytes and control uninjected oocytes;

5 Figs. 2D and 2E show the recombination between Noggin-expressing and Wise-expressing animal caps assayed for expression of Krox 20 (Fig. 2D) or *en2* (Fig. 2E). Wise induces a ring of En2 (*en*) expression or patches of Krox20 staining in a non-cell autonomous manner in the Noggin cap. In Fig. 2D, the Noggin-injected cap was marked with FIDx, and in Fig. 2E, the Wise cap was marked with lacZ, as lineage tracers;

10 Fig. 3 shows the expression of Wise in chick and *Xenopus* embryos;

Figs. 3A-3D shows the *in situ* hybridization of chick embryos. Wise is expressed in the surface ectoderm from the level of presomitic mesoderm to the posterior end at stage 10 (Fig. 3A). Higher transcript levels are detected at stage 11 (Fig. 3B), which refine to a small posterior domain by stage 12 (Fig. 3C). In Fig. 3D, a section of Fig. 3A, in the vicinity of Hensen's node shows Wise transcripts confined to the surface ectoderm (*se*);

15 Fig. 3E shows the RNase protection of *Xenopus* embryos with stages noted above each lane. Wise is first detected at an early gastrula stage, and the expression persists into tadpole stages. ODC is a loading control;

20 Figs. 3F and 3G shows the whole mount *in situ* hybridization to *Xenopus* embryos. At stage 15 (Fig. 3F), Wise is expressed in the surface ectoderm at all anterior-posterior levels. The expression is strongest at the edge of the neural tube. At tadpole stages (Fig. 3G, stage 40), expression is localized in epibranchial placodes, lateral lines, and along the dorsal fin;

Fig. 4 shows changes in neuronal markers after blastomere injection of Wise RNA and Wise antisense morpholino oligos;

Figs. 4A-4L shows *in situ* hybridization with neural markers in stage 16-21 *Xenopus* embryos following single blastomere injections of Wise RNA (Figs. 4B, 4E, 4H, and 4K) at the 8-cell stage or antisense morpholino oligos (Figs. 4C, 4F, 4I, and 4L) at the 4-cell stage. The left panels (Figs 4A, 4D, 4G, and 4J) indicate control embryos. In most embryos, lacZ (blue staining) was co-injected as a lineage tracer. Injected sides are to the left. Probes were Sox3 (Figs 4A-4C), En2 (Figs. 4D-4F), Krox20 (Figs. 4G-4I), and Slug (Figs. 4J-4L). In Wise RNA injected embryos, the neural markers were generally displaced posteriorly. Ectopic induction of Krox20 and Slug can be seen in the forebrain region (Figs. 4H and 4K). In embryos injected with antisense morpholino oligos, these markers were unchanged;

Figs. 4M and 4N show the transverse sections at stage 16 after blastomere injection of either Wise RNA (Fig. 4M) or Wise antisense morpholino oligo (Fig. 4N). In Fig. 4M, the neural plate on the injected side was greatly expanded, which is revealed by Sox3 staining (dark blue, \*). Conversely, in the morpholino oligo-injected embryo (Fig. 4N), the surface ectoderm is thicker on the injected side (left, \*) in comparison to the right control side;

Fig. 5 shows the anterior defects after blastomere injection of Wise RNA or morpholino oligo;

Figs. 5A-5L shows *in situ* hybridization with the cement gland marker XCG at stage 16-20 (Figs. 5A-5C) and morphological phenotypes of cement gland at stage 26-40 (Figs. 5D-5F) or eye at stage 35-36 (Figs. 5G-5I), in control embryos (Figs. 5A, 5D, and 5G), Wise RNA injected embryos (5B, 5E, 5H), and morpholino oligo injected (Figs. 5C, 5F, and 5I) embryos. Blue staining shows co-injected lacZ lineage tracer. Over-expression of Wise resulted in formation of



larger cement glands (Fig. 5C). Eye formation is consistently blocked by injection of both Wise RNA (Fig. 5H) and the morpholino oligo (Fig. 5I);

Fig. 5J shows *in vitro* translation of Wise in the presence of the Wise morpholino antisense oligo. Lane 1; translation of Wise protein without morpholino oligo. Lanes 2-7; translation in the presence of the Wise morpholino oligo at concentrations of 0.1 nM, 1 nM, 10 nM, 100 nM, 1  $\mu$ M, 10  $\mu$ M, respectively. Lane 8; translation in the presence of control morpholino oligo at the concentration of 10  $\mu$ M. Wise translation is partially blocked at concentration of 1  $\mu$ M, and completely blocked at 10  $\mu$ M;

Fig. 5K shows the rescue of the eye defect resulting from injection of the morpholino oligos by co-injection of Wise RNA;

Figs. 5L-5N are the phenotypes of embryos following injection of Wise morpholino oligos throughout the whole embryo. 5L shows the range of cyclopic eye and short trunk phenotypes induced by the oligos in comparison to the control embryo (left). Section of control (Fig. 5M) and morpholino-injected (Fig. 5N) embryos at the level of eye. In the Wise morpholino-injected embryos, eyes are positioned very close to the neural tube;

Fig. 6 shows that Wise requires components of the Wnt pathway for En2 induction and stimulates translocation of  $\beta$ -catenin to the nucleus;

Figs. 6A-6C show the RT-PCR of Noggin treated animal caps assayed for En2 (en) induction. NCAM is used as a pan neural marker and Efla is a loading control. Fig. 6A shows the induction of En2 by Wnt8 or Wise RNA is blocked by dominant-negative (dn) Frizzled 8  $\Delta$ Fz8. Fig. 6B shows the induction of En2 is blocked by dn-Wnt8 (Wnt8), dn-Dishevelled  $\Delta$ Dsh(dd1), GSK3 and dn-Lef1 (LEFAN). Fig. 6C shows the induction of En2 requires signaling components of the canonical Wnt pathway but not the planar cell polarity (PCP) pathway. Wise-

mediated En2 induction is abolished by  $\Delta$ Dsh(dd1), a dominant negative form of Dishevelled for both pathways, and  $\Delta$ Dsh(DIX), which blocks the canonical pathway.  $\Delta$ Dsh(DEP) blocks the PCP pathway but has no effect on Wise induction of En.  $\Delta$ Dsh $\Delta$ N specifically activates the PCP pathway but fails to induce En in the absence of Wise, although full length dishevelled (Dsh) is able to do so;

Figs. 6D-6G show the staining for sub-cellular localization of endogenous  $\beta$ -catenin detected immunocytochemically in *Xenopus* animal caps following RNA injection of: Fig. 6D, TCF3; 6E, Wnt8+TCF3; Fig. 6F, Wise+TCF3; and Fig. 6G,  $\beta$ -catenin+TCF3. Wnt8 (Fig. 6E) and Wise (Fig. 6F) promoted accumulation of nuclear  $\beta$ -catenin;

Fig. 7 shows how Wise affects Wnt signaling;

Figs. 7A-7C show the secondary axes induced by Wnt8 are blocked by Wise. Injection of Wnt8 RNA into a ventral vegetal blastomere of 4-8-cell stage embryos induces complete secondary axis formation (Fig. 7A). Co-injecting Wise blocks formation of Wnt8-induced secondary axis (Fig. 7B), similar to the effect obtained by co-injection of a dominant negative Dishevelled,  $\Delta$ Dsh(DIX) (Fig. 7C);

Fig. 7D shows Wise functions extracellularly to block induction of siamois and Xnr3 by the Wnt pathway in ventral marginal zones. Wise blocks the ability of Wnt8 to induce Siamois and Xnr3, but does not interfere with the ability of Dishevelled (Dsh) or  $\beta$ -catenin ( $\beta$ -cat) to induce these markers;

Figs. 7E and 7F show that Wise acts as Wnt inhibitor and induces head development in the incomplete secondary axis. When BMP signaling is blocked at the ventral marginal zone by injection of a truncated BMP receptor (tBR), an incomplete secondary axis is formed (Fig. 7E).

Co-injection of tBR and Wise induces a complete secondary axis with eyes (arrows) and cement gland (Fig. 7F);

Figs. 7G-7I show that Wise blocks cell movements in Activin-treated animal caps. Control animal caps (Fig. 7G) undergo gastrulation-like movements in the presence of Activin (Fig. 7H). In Wise injected animal caps, elongation is blocked (Fig. 7I), but mesoderm induction occurs;

Fig. 8 shows that Wise interacts with the extracellular domain of Frizzled 1, 3, 7, 8; and Western blotting of COS cell extracts from cells transfected with epitope tagged protein variants. The relevant constructs transfected into COS cells that were used to prepare each extract are listed at the top of each column;

Fig. 8A shows that Frizzled binds to Wise, as well as to Wnt8;

Fig. 8B shows that Wnt8 interacts with Fz1 but not with Wise; and,

Fig. 8C shows that Wise interacts with Fz1, Fz3, Fz7, and Fz8;

Figs. 8A-8C, in the top panels are controls showing that the Myc-tagged versions of each protein are present and recognized by the anti-Myc antibody. The middle panels are controls showing the presence of proteins tagged with FLAG and recognized by the anti-FLAG antibody. The bottom panels illustrate results of immuno-precipitation using the anti-Myc antibody and Western blotting with anti-FLAG to show protein interactions. The antibodies used in each set of experiments are indicated at the left;

Fig. 9A is a schematic showing the gene structure for Wise and Sost;

Fig. 9A depicts the Neo-LacZ cassette insertion into Exon 1, which is separated from Exon 2 by an intervening intron sequence;

Fig 9B shows mouse Wise and Sost polypeptide sequences;

Fig. 9C shows Wise, Sost, and Hox A and B genes in chromosomes;

Fig. 9D illustrates the family tree map showing the relatedness of Wise and Sost to other cysteine knot family members;

Fig. 9E shows the family of cysteine knot proteins and their aligned polypeptide  
5 sequences;

Fig. 10 is a model of the Wise and SOST Exons, which express the cysteine knot structure. It depicts the 200 bp of Exon 1 and the 400 bp of Exon 2;

Fig. 11 shows the effects of Sost and Wise polypeptides on *Xenopus* embryonic development;

10 Fig. 11A shows that Wise and Sost defects lead to morphological abnormalities in *Xenopus* tadpoles;

Fig 11B is a table showing Wise and Sost effects on Noggin and Wnt8 expression in embryos;

Fig. 11C depicts Sost effects for Wnt8 and  $\beta$ -catenin with VMZ and DMZ;

15 Fig. 11D shows electrophoretic patterns for NCAM, En2 and EF1- $\alpha$ ;

Fig. 11E shows electrophoretic patterns for Siamois, Xnr3, and EF1- $\alpha$ ;

Fig. 12 shows the effect of the absence of a functional Wise polypeptide molecule upon ophthalmic development in Wise knockout mice, wherein ophthalmic and eye abnormalities developed in these mice. Immunodetection of Wise protein production in murine retinal regions  
20 was used to determine the efficacy of induced Wise mutation;

Fig. 12A shows whole eye mounts containing retinas or sections that were stained with anti-Wise antibody and FITC-conjugated second antibody;

Fig. 12B shows that in wild type mice, anti-Wise reactivity was detected as secreted Wise protein in the ganglion cell and optic fiber layers and in rods and cones. However, Wise mutant mice eyes lacked detectable anti-Wise peptide reactivity, indicating absence of Wise from tissues of these mutant mice. The Wise mutant mice appeared to have lost the majority of the optic nerve fibers and had increased rod and cone layers in the retina. Wise protein was found in the inner plexiform layer, ganglion cells and fibers, and in the rods and cone layer of a 2.5 month mouse retina;

Fig. 12C shows immunofluorescence patterns for Wise, Pax6 and 2H3 in tissue cross-sections;

Fig. 13 shows results of bone staining and bone mineral density (BMD) measurements;

Fig. 13A depicts hematoxylin and eosin (H&E) staining of cross-sections of bone tissue from 16 to 18 days post cortum (DPC) mice;

Fig. 13B illustrates the same bone regions as Fig. 13A; however, Fig. 13B left shows staining with S-35 radiolabel attached to Sost RNA probes, wherein Sost is located in osteoblasts in 16 to 18 DPC mice. Fig. 13B right also shows staining with anti-Wise peptide primary antibody and FITC-conjugated secondary antibody, and localization of Wise in hypertrophic and prehypertrophic proliferating chondrocytes;

Fig. 13C shows graphical depictions of bone density measurements and total bone weight measurements, respectively. Fig. 13C left shows that observable significant differences in BMD measurements between Wise mutant and wild type mice at certain ages. Fig. 13C right depicts total bone weight measurements. Fig. 13 generally shows both Sost and Wise genes appear to affect bone cells. Sost is expressed in osteoblasts. In contrast, Wise is expressed in periosteum, chondrocytes (proliferating, prehypertrophic and hypertrophic), but not in the growth plate;

Fig 14A shows a bilateral view of two molars with developing tooth buds on hematoxylin and eosin staining of a tooth cross-section;

Fig 14B shows a bilateral view of two molars with developing tooth buds with S-35 RNA probe-labeled Sost staining;

5 Fig 14C shows a bilateral view of two molars with developing tooth buds stained with S-35 RNA probe-labeled Wise stain for purposes of detailing the layers of the dental follicle surrounding the molar teeth;

Fig 14D shows a molar tooth bud at a higher magnification with a bilateral view of two molars on hematoxylin and eosin staining of a tooth cross-section;

10 Fig 14E shows a molar tooth bud at a higher magnification stained with S-35 RNA probe-labeled Sost stain for purposes of detailing the osteoblasts and trabecular bone adjacent to the molar tooth;

Fig 14F shows a molar tooth bud at a higher magnification stained with S-35 RNA probe-labeled Wise stain for purposes of detailing the dental follicle layers;

15 Fig 14G shows a bilateral view of two molars on hematoxylin and eosin staining of a tooth cross-section, an incisor tooth staining patterns, and the morphological features of two incisors, with the nasal crest between them, tongue, and hair follicles of the whisker pad;

Fig 14H shows incisor tooth staining patterns with S-35 RNA probe-labeled Sost stain for purposes of detailing the osteoblasts of trabecular bone;

20 Fig 14I shows incisor tooth staining patterns with S-35 RNA probe-labeled Wise stain, prominent Wise staining of incisors, hair follicles and the whisker pad are also stained with Wise labeled RNA probes;

Fig 14J shows X-ray photographs of incisor teeth in the maxilla (upper jaw) regions of the wild type mice, utilizing a 120 strain genetic background;

Fig 14K shows X-ray photographs of incisor teeth in the maxilla (upper jaw) regions of the Wise mutant mice utilizing a 120 strain genetic background, the Wise mutant jaw possesses an additional incisor tooth (i') not present in the wt mouse shown in Fig 14J, the additional tooth may originate from either an additional tooth bud or, alternatively, from a bifurcation of the original incisor;

Fig 14L shows the patterning in molar teeth observed in a wt mouse against a C57BL6 genetic background;

Fig 14M shows the patterning in molar teeth observed in a Wise mutant mouse against a C57BL6 genetic background, the additional M1 molar in the Wise mutant is present compared to the M1, M2, and M3 molars present in the wt mouse in Fig 14L;

Fig 14N shows the patterning in molar teeth observed in a wt mouse against a 129 background; and

Fig 14O shows the patterning in molar teeth observed in a Wise mutant mouse against a 129 background, abnormalities are present compared to the wt mouse of Fig 14N.

## DETAILED DESCRIPTION

The present invention relates to a family of nucleic acid molecules, which encode polypeptides that bind to LRP and likely regulate the Wnt pathway and, resultingly, regulate bone deposition. The polypeptides will also regulate ocular and tooth development. The present invention further relates to proteins and polypeptides, or amino acid sequences, expressed from the family of nucleic acid molecules, which regulate bone deposition through LRP interaction.

In particular, a nucleic acid molecule family, which includes the Wise and Sost genes, can be used with the present invention, as well as the family of amino acid sequences expressed therefrom. When the above family of amino acid sequences, including Wise and Sost, are allowed to bind to an LRP protein, bone deposition is regulated. When the family of amino acid sequences are prevented from binding to an LRP protein, deposition of bone will increase.

Antisense RNAs or oligonucleotides can be used to block translation of mRNA related to or translated from the above described nucleic acid molecules—in particular, the LRP binding family of amino acid sequences and polypeptides can cause increased bone deposition and likely activate the LRP/Wnt pathway. Similarly, inhibitor peptides and polypeptides prevent the above family of amino acid sequences from binding to an LRP to thereby increase bone deposition. As such, the present invention includes the above listed methods, nucleic acid molecules, amino acid sequence or polypeptide molecules, as well as related compositions and methods designed to prevent or inhibit binding by the LRP binding protein family to LRP. These tools can also be used to effect phenotypic changes. Specifically, mutants versions of Wise or Sost will cause phenotypic changes. Kits are described for detection of the above native nucleic acid molecules and amino acid sequence molecules. Kits are described for detection of mutant or variant forms of the aforementioned nucleic acid molecules, detection of expressed polypeptides or proteins, and measurement of corresponding levels of protein expression.

The novel Wnt inhibitor, Wise, has been isolated in the present invention. Wise affects craniofacial anterior-posterior patterning. The biochemical function of craniofacial A-P patterning is generally addressed in the present invention. Previously, it was shown that when chick somites were transplanted to more anterior locations, an anterior shift in Hox gene expression was observed. This shift in expression resulted in a posteriorization of the more



anterior neural tissue. A screen for molecules involved in this process lead to the isolation of Wise. Wise is a secreted molecule that, until now, has not been shown to share much homology to any known molecules. Its gene structure contains two exons (200 and 400bp) with a large 2.5Kb intron (Fig. 10). The second exon encodes a cysteine knot motif, which bears some  
5 homology to known DAN, and CCN family members (Figs. 9, 10, 11). Wise is mapped to Human chromosome 7p21.1, which in turn is linked to the HoxA cluster by 10.6Mb (Fig. 9C). The four mammalian Hox clusters are thought to have evolved from a single cluster, as in *Drosophila*, therefore other clusters were searched for a possible Wise family member. Nothing was found that linked to the HoxD cluster, however, it was found that both HoxB and HoxC  
10 clusters had an ORF that was examined further. The HoxC cluster ORF, at 4Mb upstream shares homology to the CCN family. The HoxB cluster contained an ORF at 5Mb upstream. The HoxB ORF encodes a known gene, Sost. Sost was positionally cloned because of a familial mutation affecting bone density. Sost and Wise both share the same gene structure, and produce a secreted protein whose second exon (70% homologous) encodes for a cysteine knot. Unlike the  
15 known cysteine knot from DAN or CCN family members, Wise and Sost cysteine knots contain 8 cysteines instead of 9 like CCN and DAN families. Other molecules, Mucin2 and VWF have cysteine knots containing 10 cysteines, but are arranged in a manner similar to both the CCN and DAN family. DAN and CCN cysteine knots share about 50% homology to those of Wise and Sost. In addition to the cysteine knot domain, CCN proteins also encode for Insulin binding,  
20 Von Willderbrand, and TSP1 domains. However, the DAN family appears to only encode for a cysteine knot domain. Other genes that encode a cysteine knot domain include Slits, VWF, Mucins, and NDP.

A new Wise family member, Sost, has been characterized herein. Both Wise and Sost are linked to a Hox cluster further supporting Hox cluster duplication hypotheses. Sost functions like Wise to inhibit the Wnt pathway, however, unlike Wise, Sost is unable to induce En2 expression. The inability to induce En2 is very similar to other cysteine knot family members, like CTGF and Nov.

A family of genes and related proteins or polypeptides was isolated, which likely bind to LRP and likely regulates the LRP/Wnt pathway and causes regulation of bone deposition. The family of genes includes NDP, Dan, Caronte, PDGF, Wise, Sost, Cereberus, Gremlin, CTGF, Soggy, Dkk1, Cyr61, Dkk2, Dkk3, Dkk4, Nov, Mucin, Slit, OH, WISP, and CCN. Proteins expressed therefrom form a related amino acid sequence family. These nucleic acid molecules include sequences identified as SEQ ID NOs 1-44, 96-103, 105, 108, 110-113, and 126-128, and amino acid sequences identified as SEQ ID NOs 45-95, 104-107, 109, 114-125. When the above genes of the family are turned off, or mutagenized, the LRP pathway typically is not regulated and deposition of bone will increase. More particularly, the gene-encoded proteins do not bind to LRP, resulting in increased bone deposition. The gene-expressed proteins can be blocked to prevent regulation of the LRP pathway. Thus, the present invention relates to nucleic acid molecules and amino acid sequences and other tools and methods used to inhibit, block or deactivate binding of the LRP binding family to LRP. Inhibition of Wnt signaling can occur with resultant blocking or deactivation of the LRP binding family to LRP.

Related to this, it is known that mutant Wise and Sost polypeptides cause phenotypic changes in bone deposition, ocular development and tooth development. Regardless of interaction with LRP it is determined that mutants of Sost or Wise, or antibodies which attach to Sost or Wise, will cause phenotypic changes.

The above gene family and related proteins can not only be characterized as binding to or blocking binding to LRP, but as a gene family that expresses related proteins that each possess at least one cysteine knot. The cysteine knot is generally formed by 8 cysteine residues, which are readily conserved. However, other knots may have fewer or more residues. Typically, a guanine  
5 is part of the structure and conserved. Guanine will, along with two other amino acids, separate two cysteines located in one arm. For example, the gene family contains the genes Sost, Wise, Dkk1, Dkk2, OH, WISP, and CTGF. These genes include an exon region (*e.g.*, Exon 2), which expresses a protein or amino acid sequence molecule, which has a cysteine knot and binds to LRP.

10 Wise genes and polypeptides that have been specifically isolated, including wild types, alleles, mutants, synthetic versions and any other related homologous nucleic acid sequences, are used herewith. Wise contains two exons, with Exon 2 considered the most important. Exon 2, when expressed, produces a polypeptide that has a cysteine knot.

The present invention includes the LRP binding family of polypeptide molecules, such as  
15 Wise, Sost, Dkk1, Dkk2, and CTGF, that binds to LRP, which will, in turn, likely bind to Wnt. The LRP proteins and related genes will include LRP 1-11, and Arrow. LRPs that have been found to be specifically related to the present include LRP1,2,5, and 6. Available LRP nucleic acid sequence, are SEQ ID NOs 29-43, polypeptide SEQ ID Nos 67-88.

The present invention also relates to antisense RNA (asRNA) complementary to an  
20 mRNA from the LRP binding nucleic acid family, in particular Wise and Sost, whereby the asRNA will inhibit the members. An RNA may also be used to induce post-transcriptional gene silencing. This RNAi will cause translation of the gene family to cease. Any RNA/DNA that is complementary to the mRNA related to the discussed gene family, can be used to destroy a

family member. Other mutants include point frame shift, deletion, truncated, base substituted, and less of function mutations. The loss of function mutations are made with a stop codon.

Additionally, a polyclonal or monoclonal anti-peptide antibody to the cysteine knot antigenic region may be used for detection or inhibition. This antibody would inhibit interaction with

5 LRP. The antibody can also be directed to the entire Wise or Sost polypeptide. A point mutation may be made in a nucleic acid sequence member of the gene family, whereby the expressed protein or polypeptide cannot bind LRP. Alternatively, an antisense oligonucleotide can be used, which will prevent translation of mRNA and thereby inhibit binding to LRP. An anti-polypeptide antibody can be used to bind to LRP and prevent binding with a cysteine knot  
10 protein, preferably functioning by a steric hinderance mechanism.

Mutant alleles of the LRP binding gene family can express a protein or amino acid sequence that will not bind LRP and thereby increase bone deposition. As discussed, expression of such a mutant can be therapeutically desirable, especially when used as a method for producing stronger bones or increased recovery from bone disease. Thus, the present invention  
15 relates to mutants of the listed gene family. The present invention includes administration of such mutant polypeptide products that can result in increased bone deposition.

Antibodies, which specifically bind to the above proteins and probes for isolating the proteins or nucleic acid molecules, are further part of the present invention. Fab fragments can be derived from the antibodies. Yet another part of the present invention relates to methods for  
20 increasing bone deposition by preventing the protein family from binding to an LRP and, in turn, likely regulating the Wnt pathway. The invention includes methods for blocking expression of the nucleic acid molecules, and methods for preventing the amino acid sequences from binding to Wnt or LRP. Kits are also part of the invention which detect mutants and non-mutants of the

nucleic acid molecules, and their expressed amino acid sequences or polypeptide molecules. As such, the present invention includes diagnostic and therapeutic methods and kits for the prediction, assessment, and regulation of bone deposition.

Nucleic acid sequences complementary to the previously listed nucleic acid molecules, preferably the mutants, of the gene family may also be used with the present invention. As expected, such a complementary nucleic acid sequence is one that can be expressed to form a protein or amino acid sequence that binds to LRP and regulates bone deposition. The complementary sequence can also be used to prevent binding of LRP and, thus, increase bone deposition. A complementary nucleic acid sequence from a member of the LRP binding gene family can be made to produce an expressed polypeptide that can impact binding to LRP and ultimately regulate bone deposition. Further, degenerate variants of the sequences may be used. Also, isolated nucleic acid molecules that encode the LRP binding family protein or amino acid sequence may be used in the present invention.

Nucleic acid molecules homologous to the wild type nucleic acid molecules, and the mutant nucleic acid molecules, may be used to regulate or cause increased bone deposition. The homologous nucleic acid molecules are identified using a BLAST (Basic Alignment Search Tool) (NCBI) sequence method. Suitable homology will include those nucleic acid molecules that are 50% homologous to the listed mutant alleles, or non-mutants. More preferably, the homology will be 60% and, even more preferred, 75% homologous to the mutant alleles, or non-mutants. The most preferred homologous nucleic acid molecule will be 90% homologous to the mutant alleles, or non-mutants (*i.e.* wild type), in particular, Wise, Sost, and mutants thereof. Homologous nucleic acid molecules may be derived from animals, including, but not limited to, humans, non-human mammals, amphibians, and insects.

Isolated nucleic acid sequences, such as oligonucleotides, can be derived from the nucleic acid molecules, which are the active portions of the molecules, to bind with LRP, mRNA, or ultimately prevent binding of the LRP protein. Such oligonucleotides are a part of the present invention. The active region, which forms the oligonucleotide molecules, includes the cysteine  
5 knot region. More particularly, a region which expresses a cysteine knot sequence that binds to LRP can be used. Conversely, oligonucleotides related to the mutant forms of the genes can be used to prevent regulation of bone deposition.

Expression vectors, which regulate bone deposition, can be formed that contain the above-discussed nucleic acid molecules, using known procedures. A promoter can be operably  
10 linked to the isolated nucleic acid molecule to form the expression vector. Any promoter can be used which causes expression of the nucleic acid molecule, and can be switched on and off. It is further preferred to include a marker with the vector. Suitable vectors include DNA vectors, plasmid vectors, and shuttle vectors.

Vectors are formed from both the isolated nucleic acid sequences and the mutant  
15 versions of the isolated nucleic acid sequences. The vectors include expression, cloning, and viral vectors. Other available vectors include fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors. Also, prokaryotic and eukaryotic vectors may be used. Specific prokaryotic vectors that may be used in the present invention include pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280,  
20 pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT. Specific eukaryotic vectors that may be used herein include pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo,

pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis. As mentioned, a variety of promoters may be used with the vector, as well as any of a variety of selectable markers. Available markers include antibiotic resistance genes, a tRNA gene, auxotrophic genes, toxic genes, phenotypic markers, colorimetric markers, antisense oligonucleotides, restriction endonuclease, enzyme cleavage sites, protein binding sites, and immunoglobulin binding sites. Specific selectable markers available include LacZ, neo, Fc, DIG, Myc, and FLAG.

Once the vectors are formed, they can be used to transfect a host cell, whereby a transgenic host cell will be produced that incorporates a vector that expresses the selected nucleic acid molecule, which prevents or causes bone deposition through interaction with the LRP. Such bone deposition may likely involve interaction with the Wnt pathway. Methods for transfecting the host cell are well known to those of skill in the art, and comprise culturing the vectors with the host cells.

The host cell can be derived from any of a variety of eukaryotic cell origins, including animal-, mammalian-, amphibian-, or insect-derived cells. More preferably, the host cells are derived from non-human mammals and humans. The preferred host cell is an osteoblast/osteoclast, chondrocytes.

Any of a variety of host cells, including prokaryotic and eukaryotic cells, can be transfected with the vectors previously mentioned. Prokaryotic host cells include Gram-negative and Gram-positive bacteria may be transfected with any of the variety of the vectors previously mentioned. Available bacteria include Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas. A preferred Gram-negative bacterium is Escherichia coli. Eukaryotic vectors can be used to transfect eukaryotic host cells

including yeast, plant, fish, mammalian, human, mouse, frog, or insect cells. Specific host cells that can be transfected include ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, chondrocytes, and human or mammalian bone marrow stroma. As such, the present invention includes host cells transfected with any of the previously mentioned vectors.

A transgenic animal can be formed using the present invention. In particular, transgenic non-human animals can be formed by insertion of the wild type or mutant nucleic acid molecules into cells of a host animal. The insertion of nucleic acid molecules into host animal cells can occur by a variety of methods including but not limited to transfection, particle bombardment, electroporation, and microinjection. Insertions can be made into germ line, embryonic, or mature adult host animal cells.

The proteins or amino acid sequences expressed by the nucleic acid molecules, related mutants, and the listed nucleic acid molecules can activate LRP/Wnt and can be isolated and purified. Additionally, the mutants, asRNA molecules, as oligonucleotides, and anti-peptide antibodies can be developed and used to prevent binding to LRP or binding of Wnt or Sost. The proteins or amino acid sequences from both the non-mutant and mutant nucleic acid molecules can also be isolated and purified. Such isolation and purification include known procedures and methods, including affinity chromatography or purification, as well as other methods. The isolated proteins include those listed herein. Additionally, suitable proteins or amino acid sequences include those that bind to LRP and Wnt, and prevent or cause activation, dependent upon the desired outcome.

Proteins, which are 90% homologous with the polypeptides listed in SEQ IDs are also included. As would be expected, polypeptides or proteins that are 50% homologous to the



polypeptides may also be used, with proteins 60% homologous more preferred. A polypeptide that is 75% homologous to SEQ ID NOs 45-95, 104-107, 109, and 114-125 is even more preferred. As such, any of a variety of polypeptides may be used, as long as they are expressed by an LRP binding family member, Sost Wise, or homologous nucleic acid molecule, and  
5 prevent influence Wnt, Bone deposition, tooth development or ocular development. More preferably, mutants will be used. Resultingly, the proteins will cause increases of bone deposition to occur. Non-mutant, homologous amino acid sequences may be used. The extent of homology will be identical to that previously described above. Thus, sequences that are 50% homologous to the proteins or amino acid sequences may also be formed. More preferably, the  
10 sequences will be 75% homologous, and even more preferably, 90% homologous to the proteins.

Probes, which can be used to isolate, identify, and characterize the above proteins and/or genes, can be formed from such proteins or genes. The probes include cDNA, mRNA, and monoclonal and polyclonal antibodies. All the probes are formed using known procedures. Probes, which are 50% homologous to the proteins or amino acid sequence, may also be formed.  
15 More preferably, the probes will be 75% and, even more preferably, 90% homologous to the above proteins. The formula used to determine the homology of the probes is a BLAST sequence.

Antibodies, which specifically bind to the above-listed proteins, are part of the present invention. Additionally, hybridomas that produce such antibodies are used herewith. In addition  
20 to protein probes, cDNA probes may be formed, which are comprised of isolated nucleic acid molecules previously discussed. As such, any antibody that binds specifically to a Wnt binding family member, may be used. Antibodies that selectively bind to an epitope in the receptor-

binding domain of the LRP/Wnt binding mutant protein may also be used. A non-mutant or wild type epitope may also be used.

A kit for detecting a LRP binding gene, or related nucleic acid molecule, can be formed. The kit will preferably have a container and a nucleic acid molecule, which includes any of the  
5 mentioned sequences.

A kit for detecting a LRP binding protein or amino acid molecule can also be formed. The kit will preferably have a container and a nucleic acid molecule, which includes any of the mentioned sequences.

The family of genes and proteins can be used as tools to develop asRNAs and  
10 polypeptides, which regulate LRP/Wnt.

Neural patterning in embryogenesis involves signaling between the neural plate and surrounding tissues. To investigate this process, a functional screen was performed using a cDNA library derived from chick tissues surrounding the neural tube. Activities that alter anteroposterior (A-P) character of neuralized *Xenopus* animal caps were assayed for, and a novel  
15 gene was identified, Wise, which was expressed in surface ectoderm. Wise encodes a secreted protein capable of inducing posterior neural markers. Importantly, the phenotypes arising from ectopic expression of Wise resemble those affected when Wnt signaling is altered. Induction of posterior markers by Wise likely requires components of the canonical Wnt pathway, showing that it activates the Wnt signaling cascade. In contrast, in other assays, such as secondary axis  
20 induction, Wise inhibits Wnt signaling. Wise protein interacts with LRP receptors, but not with Wnt, demonstrating that Wise is a novel ligand for LRP, which either activates or inhibits the signaling pathway. Hence, Wise differentially influences the Wnt signaling cascade in a context-

dependent manner. These activities provide a novel mechanism that integrates and modulates the balance of Wnt signaling.

The following are definitions for terms used herein.

An animal cap is a pigmented animal hemisphere of the amphibian blastula. The vegetal  
5 becomes endoderm and part of the animal pole becomes ectoderm. In most animal oocytes the nucleus is not centrally placed, and its position can be used to define two poles. That nearest to the nucleus is the animal pole, and the other is the vegetal pole, with the animal-vegetal axis between the poles passing through the nucleus. During meiosis of the oocyte, the polar bodies are expelled at the animal pole. In many eggs, there is also a graded distribution of substances  
10 along this axis, with pigment granules often concentrated in the animal half and yolk region, when present, largely situated in the vegetal half.

The anterior-posterior axis is the body axis extending from the anterior to the posterior pole of a bilaterally symmetric embryo (or animal).

Blastomere is one of the cells produced as the result of cell division and cleavage, in the  
15 fertilized egg.

Blastula is the stage of embryonic development of animals near the end of cleavage but before gastrulation. In animals where cleavage or cell division involves the whole egg, the blastula usually consists of a hollow ball of cells.

Bone is continually deposited by osteoblasts. Normally, bone deposition and absorption  
20 are equal.

DNA cassette is a deoxyribonucleic acid (DNA) sequence that can be inserted into a cell's DNA sequence. The cell in which the DNA cassette is inserted can be a prokaryotic or eukaryotic cell. The prokaryotic cell may be a bacterial cell. The DNA cassette may include one

or more markers, such as Neo and/or LacZ. The cassette may contain stop codons. In particular, a Neo-LacZ cassette is a DNA cassette that can be inserted into a cell's DNA sequence located in a bacterial artificial chromosome (BAC). Such DNA cassettes can be used in homologous recombination to insert specific DNA sequences into targeted areas in known genes.

5           The ectoderm is the germ layer that gives rise to the epidermis and nervous tissue.

          The endoderm is the germ layer that gives rise to the respiratory organs, gut, and the gut accessory glands.

          Gastrula is the stage of embryonic developments in animals when gastrulation occurs, and follows the blastula stage.

10          Gastrulation is the process by which cells of the blastoderm are translocated to new positions in the embryo, producing the three primary germ layers.

          The germ layer is defined as the main divisions of tissue types in multicellular organisms. Diploblastic organisms (*e.g.*, coelenterates) have two layers, ectoderm and endoderm; triploblastic organisms (*i.e.*, all higher animal groups) have mesoderm between these two layers.

15          Germ layers become distinguishable during late blastula/early gastrula stages of embryogenesis, and each gives rise to a characteristic set of tissues, the ectoderm to external epithelia and to the nervous system, for example, although some tissues contain elements derived from two layers.

          Mesoderm is defined as the middle of the three germ layers; which gives rise to the musculo-skeletal, vascular, and urinogenital systems, to connective tissue (including that of  
20    dermis) and contributes to some gland formation.

          Neural plate is defined as a region of embryonic ectodermal cells, called neuroectoderm, that lie directly above the notochord. During neuralation, the neuroectoderm changes shape, so

as to produce an infolding of the neural plate (*i.e.*, the neural fold) that then seals to form the neural tube.

The neural tube is the progenitor of the central nervous system.

Somites are defined as the blocks of tissue in the trunk derived from the originally  
5 unsegmented paraxial mesoderm.

Small molecules are defined as regulatory polypeptide or nucleic acid molecules that cause detectable changes in protein-protein interaction systems that may also affect one or more phenotypic changes. Interaction systems include, but are not limited to, Wise and Sost protein interaction with LRPs, the Wnt pathway, Engrailed, and Frizzled. These small molecules may  
10 operatively function by structural similarity to and competitive inhibition with native molecules *in vitro* or *in vivo*. Phenotypic changes may include observed changes in such parameters as bone deposition or bone mineral density, tooth development, and ocular development. Small regulatory polypeptide molecules include, but are not limited to, antibody fragments such as Fab, F(ab)<sub>2</sub>, Fv, and antibody combining regions that bind with either Wise, Sost, or LRP; and  
15 shortened Wise, Sost or LRP polypeptide sequences. Small regulatory nucleic acid molecules include, but are not limited to, antisense RNA sequences that interfere with Wise, Sost, or LRP function; and truncated Wise, Sost or LRP nucleic acid sequences that encode shortened polypeptides that interfere with Wise, Sost or LRP function. An antisense Wise RNA is complementary to Wise sense RNA and operatively binds to it in a cell to prevent translation of  
20 native protein. A truncated Wise nucleic acid sequence encodes a shortened Wise polypeptide that can potentially competitively bind to LRP to prevent native Wise protein binding.

The vegetal pole is the surface of the egg opposite to the animal pole. Often the cytoplasm in this region is incorporated into future endoderm cells.

A vector is a self-replication DNA molecule that transfers a DNA segment to a host cell.

A host organism is an organism that receives a foreign biological molecule, including an antibody or genetic construct, such as a vector containing a gene.

Chimera is an individual composed of a mixture of genetically different cells. The genetically different cells of chimeras are required to be derived from genetically different zygotes.

Mutant is an organism bearing a mutant gene that expresses itself in the phenotype of the organism. Mutants include both changes to a nucleic acid sequence, as well as elimination of a sequence. In addition polypeptides can be expressed from the mutants.

Plasmids are double-stranded, closed DNA molecules ranging in size from 1 to 200 kilobases. Plasmids are vectors for transfecting a host with a nucleic acid molecule.

An amino acid (aminocarboxylic acid) is a component of proteins and peptides. Joining together of amino acids forms polypeptides. Polymers containing 50 or more amino acids are called proteins. All amino acids contain a central carbon atom to which an amino group, a carboxyl group, and a hydrogen atom are attached. Polypeptides can be referred to when a protein is less than 500 amino acids.

A nucleic acid is a nucleotide polymer better known as one of the monomeric units from which DNA or RNA polymers are constructed, it consists of a purine or pyrimidine base, a pentose, and a phosphoric acid group.

A gene is a hereditary unit that has one or more specific effects upon the phenotype of the organism that can mutate to various allelic forms.

A polypeptide is a polymer made up of less than 50 amino acids.

Knockout is an informal term coined for the generation of a mutant organism (generally a mouse) containing a null allele of a gene under study. Usually the animal is genetically engineered with specified wild-type alleles replaced with mutated ones.

5 Allele is a shorthand form for allelomorph, which is one of a series of possible alternative forms for a given gene differing in the DNA sequence and affecting the functioning of a single product.

Wild type is the most frequently observed phenotype, or the one arbitrarily designated as “normal”. Often symbolized by “+” or “wt.”

10 Finally, the phenotypes observed in Wise mutants are similar to that of Sost mutants. Some phenotypes examined in the Wise mutant may explain Sost phenotypes, *i.e.* loss of retinal nerve fibers may be reason for optic nerve atrophy. Interestingly, it has been demonstrated that Wise inhibits the Wnt pathway by binding to an area encompassing the first two YWTD propeller domains of LRP. In humans the autosomal recessive disorder OPPG has been mapped  
15 to the area upstream of the first YWTD propeller domain of LRP5. Also, LRP5 is found to be expressed in osteoblasts and in retinal cells of *Xenopus* embryos. The same expression pattern was found for humans. It has been demonstrated that the loss of LRP5 function leads to very low peak bone mass and visual loss. Thus, early during bone development, Wise may be acting to inhibit Wnts through LRP5; and later, the inhibition of Wnts may be the function of Sost.

20

## EXAMPLES

### Example 1.

Functional screens in *Xenopus* were performed with the aim of identifying factors derived from tissues surrounding the neural tube that alter A-P patterning in Noggin-treated animal caps. Two clones were isolated, one encoded a truncated  $\beta$ -catenin and the other a novel secreted protein, which was named Wise. Isolation of the two clones is described below.

5 Fig. 1A provides an overview of how factors which impacted patterning were determined. Chick embryo somites, which are capable of transforming pre-otic rhombomeres into a more posterior neural tissue were collected together with overlying ectoderm and underlying endoderm. mRNA was collected from the tissue, which was then used to make a cDNA library. This provided a source of putative posteriorizing factors.

10 The cDNA library was made from stage 8-13, (Hamburger and Hamilton, 1951) chick embryos using tissues surrounding the neural tube (Fig. 1A) from axial levels capable of inducing Hoxb9 expression in grafting experiments (Itasaki et al., 1996). The library contained 250,000 un-amplified clones, and 50,000 of these were divided into 100 pools (500 clones per pool). For initial screening, 10 pools were mixed to prepare a single large DNA pool (5,000 clones) used to synthesize capped RNA. Size-selected (>1kb) cDNAs were directionally  
15 inserted into a modified 64T vector (Tada et al., 1998).

*Xenopus* eggs were obtained, fertilized, cultured, and injected with the synthesized RNA, as previously described (Jones and Smith, 1999). In the first round of screening, 250 picogram (pg) of Noggin RNA and 12 nanograms (ng) of library RNA were injected into each blastomere  
20 of 2-cell state *Xenopus* embryo. To examine embryo phenotypes, RNA was injected into specific blastomeres, together with lacZ or FIDx (Molecular Probes) as a lineage tracer. Markers were assayed with *in situ* hybridization.



Following co-injection of Noggin RNA with pools of RNA from the cDNA library, the induction of posterior markers was monitored in animal caps by assaying for expression of En2, Krox20, and Hoxb9, which mark the midbrain, hindbrain, and spinal cord, respectively (Figs. 1B and 1C). Myosin was also used as a marker for mesoderm induction, which allowed focus on  
5 pools that influence neural patterning in the absence of mesoderm.

Explants (excised tissue) were processed for RT-PCR to detect region-specific neural markers. The primers for Efl $\alpha$ , NCAM, Otx2, En2, Krox20, Hoxb9, Myosin light chain and Muscle actin were used.

It was observed in pool 5, that En2 was induced in the absence of mesoderm (Fig. 1B).

10 Successive rounds of sub-division and sib selection identified the clones responsible for this activity. From this pool, two distinct clones were isolated. One clone encoded an amino-terminally truncated form of  $\beta$ -catenin, a cytoskeletal component, and an intracellular target of the Wnt pathway. This result was consistent with data demonstrating that  $\beta$ -catenin has an ability to induce posterior neural markers in animal caps when co-injected with Noggin. The N-  
15 terminal truncation in the clone removed the first 87 amino acids, which included the sites for phosphorylation by GSK3 $\beta$ , which accelerated degradation of  $\beta$ -catenin protein. Therefore, the clone encoded a stable form of  $\beta$ -catenin able to stimulate Wnt signaling.

The second clone proved to encode a novel protein. Based on its characterization and relationship to Wnt signaling detailed in the study, the clone's gene was designated Wise (Wnt,  
20 inhibitor/activator in surface ectoderm). In the animal cap assays, injection of Wise RNA, together with Noggin, demonstrated that increasing concentrations of Wise progressively induced more posterior markers (En2 and Krox20) in the absence of mesoderm (Fig. 1C).  
Noggin equal to 500 pg and Wise equal to 150, 300, 600 and 1200 pg were injected. Wise alone

exhibited no neural-inducing activity (no NCAM induction) and no ability to induce mesoderm, as confirmed using Myosin (Fig. 1C), Brachyury, Wnt8, and Xhox3 as markers. It was observed that increasing amounts of Wise RNA (150, 300, 600, and 1200 pg) progressively induced more posterior neural markers in the presence of Noggin. Wise DNA and RNA were obtained using  
5 standard molecular biology methods. Sambrook et al., Molecular Cloning: a Laboratory Manual, 3<sup>rd</sup> ed., Cold Spring Harbor, N.Y., Cold Spring Harbor Laboratory Press (2001).

For explant recombination assays, 500 pg of Noggin was injected into one set of embryos and 1 ng of Wise injected into a separate set. For lineage tracing, either FIDx was injected, along with Noggin RNA, or 100 pg of lacZ RNA was co-injected with Wise. Caps were cut at  
10 stage 8, combined and cultured for assay at stage 25.

### Example 2.

To isolate a frog clone, *Xenopus* stage 25 embryos were collected and a cDNA library was formed. This was used as a template for RT-PCR. Using degenerate primers, designed on the basis of conserved regions between chick and mouse Wise, ~500 bp fragments were sub-  
15 cloned into pBluescriptIIKS (Stratagene) and sequenced. The degenerate primers used were upstream, SEQ ID NO 129: 5'-GCTTT(T/T)AA(A/G)AA(C/T)GATGCCAC-3'; and downstream, SEQ ID NO 130: 5'-GTGAC(T/C)AC(T/G/A)GT(T/G)ATTTTGTA-3'. Two different clones in the frog were identified (XWise-A and XWise-B) presumably resulting from the pseudotetraploid *Xenopus* genome. For each clone, 5' and 3' flanking sequences were  
20 identified by PCR using a *Xenopus* stage 35 cDNA library. Standard PCR methods are described in U.S. Pat. No. 4,683,195; U.S. Pat. No. 4,683,202; Saiki et al., Science 230:1350-1354 (1985); Innis et al., PCR Protocols: A Guide to Methods and Applications, Academic Press, Inc., San Diego, Calif. (1990).

The predicted amino acid sequence of XWise-A was used for comparison with other species which are listed in Fig. 2A, which shows Wise as a conserved secreted protein. Various EST databases were searched, with the predicted amino acid sequences then aligned in Fig. 2A. The predicted amino acid sequence of Zebrafish, *Xenopus*, chick, mouse, and human Wise proteins were compared.

The predicted Wise protein, SEQ ID NO 45, consists of 206 amino acids and contains cysteine knot-like domains. These cysteine knot domains are found in a number of growth factors, as well as in Slit, Mucin, and CCN (Cefl0/Cyr61, CTGF and Nov) family members (Bork, 1993). Among these, the C-terminal domain of the CCN family members showed the highest homology to Wise, but other motifs conserved within the CCN family were absent in Wise (Fig. 2B). Hence, Wise is related to, but not a member of, the CCN family. A homology search revealed that Wise showed the highest amino acid identity (38%) to Sclerostin (Sost), identified by positional cloning of the gene mutated in sclerosteosis (Brunkow et al., 2001).

Wise was further analyzed, as shown in Fig. 2B. The shaded boxes in Fig. 2B indicate three blocks ( $\Delta 1$ ,  $\Delta 2$ ,  $\Delta 3$ ) deleted separately for functional analysis. This was done to investigate if the conserved regions were required for functional activity of Wise, three separate deletions were generated, and their ability to induce En2 expression in Noggin-injected animal caps was tested. The variant that deleted 19 amino acids outside of the CT domain ( $\Delta 1$ ) retained the ability to induce En2. In contrast, two deletions corresponding to different parts of the Slit homology domain ( $\Delta 2$  and  $\Delta 3$ ) abolished the ability of Wise to induce En2, demonstrating that these regions were necessary for Wise function.

**Example 3.**

A signal sequence motif is present at the N-terminus of Wise, and its secretion was confirmed by Western blotting following expression of an HA-tagged version of the protein in *Xenopus* oocytes (Fig. 2C) and COS cells. More particularly, Wise was injected in an amount equal to 30ng/embryo. Western blot analysis detected HA-tagged Wise protein secreted into the medium following RNA injection into oocytes. Fig. 2C, related to the control of uninjected oocytes. Secretion of Wise was confirmed by expression of an HA-tagged version of the protein in *Xenopus* oocytes and COS cells. The protein was detected in both cell extracts and the culture medium (Fig. 2C). It was observed that Wise encoded a signal sequence motif at its N-terminus, suggesting that the protein is secreted.

Further, the ability of Wise to posteriorize neural tissue in a cell non-autonomous manner was tested by using a tissue recombination assay in which a Wise-expressing animal cap was combined with a noggin-expressing animal cap. It was found that both En2 and Krox20 were induced in discrete domains in the Noggin caps (Figs. 2D and 2E). Noggin was injected in an amount equal to 500 pg and Wise equal to 600 pg. Hence, it was determined Wise has the ability to induce posterior markers at a distance.

Subsequently, the ability of Wise to posteriorize tissues in a cell non-autonomous manner was tested. Recombination between Noggin-expressing and Wise-expressing animal caps were assayed for expression of Krox20 or En2, Figs. 2D and 2E respectively. Wise induced a ring of En2 (en) expression or patches of Krox20 staining in a non-cell autonomous manner in the Noggin cap. In Fig. 2D, the Noggin injected cap was marked with FIDx, and in 2E, the Wise cap was marked with lacZ as lineage tracers. Using a tissue recombination assay in which a Wise-expressing animal cap was recombined with a Noggin expressing animal cap, it was found that

both En2 and Krox20 were induced in the Noggin caps (Figs. 2D and 2E). As such, it was determined that Wise has the ability to induce posterior markers at a distance through the induction of Wnt.

#### Example 4.

5           The following Example analyzes the expression of Wise in chick and *Xenopus* embryos. Whole mount *in situ* hybridization analysis and sections in stage 9-12 chick embryos revealed that Wise was expressed in a dynamic manner in the surface ectoderm (Figs. 3A-3D). Expression was detectable first at stage 9. Expression was localized in the posterior surface ectoderm overlying the presomitic mesoderm, wherein somites were formed by stage 10-11 (Figs. 3A, 3B, and 3D). Figs. 3A-3D show *in situ* hybridization of chick embryos. Wise was expressed in the surface ectoderm from the level of presomitic mesoderm to the posterior end at stage 10, Fig. 3A. Higher transcript levels are detected at stage 11, Fig. 3B, which refine to a small posterior domain by stage 12, Fig. 3C. This is shown by the red stain in the Fig. 6. A section shown in Fig. 3D, in the vicinity of Hensen's node, showed Wise transcripts confined to the surface ectoderm (se). This is shown by the arrow. Expression decreased rapidly during stages 12-13, and resolved into a small posterior domain (Fig. 3D). This expression profile suggested that the original Wise cDNA was derived from the ectodermal part of the tissue used to make the library (Fig. 1A).

20           In an RNase protection assay, *Xenopus* Wise expression was weakly detected initially at gastrula stages (stage 10), and expression persisted into tadpole stages (Fig. 3E). Fig. 3E shows an RNase protection assay of *Xenopus* embryos with stages noted above each lane. Wise is first detected at an early gastrula stage, persisting into tadpole stages. ODC was a loading control. In later stage chick embryos, Wise was expressed in branchial arches and other specialized tissues,

including feather buds. A similar pattern was observed in *Xenopus* embryos. Wise was expressed in the surface ectoderm, but had a broader domain along the A-P axis, in comparison to chick (Fig. 3F). Figs. 3F and 3G show the whole mount *in situ* hybridization to *Xenopus* embryos. At stage 15 (Fig. 3F), Wise is expressed in the surface ectoderm at all anterior-posterior levels. The expression is strongest at the edge of the neural tube. At tadpole stages (Fig. 3G, stage 40), expression was localized in epibranchial placodes, lateral lines, and along the dorsal fin.

This data showed that Wise caused posterior development. It also showed the stages of development when Wise had the strongest effect.

#### 10 **Example 5.**

The present Example relates to changes observed in neuronal markers after blastomer injections of Wise RNA and Wise antisense morpholino oligos (Fig. 4).

Morpholino antisense oligos were designed against the beginning of the coding region of *Xenopus* Wise-A and B. The sequences were: A (SEQ ID NO 131), 5'-  
15 AGCACTGGAGCCTTGAGACAACCAT-3'; B (SEQ ID NO 132), 5'-  
AGCAGTGAAGCCTTGAGACAACCAT-3'. A 1:1 mixture of these oligos was diluted in PIPES (5mM) buffered water and used for injection. *In vitro* translation of Wise RNA was inhibited at oligo concentrations of between 1-10  $\mu$ M, which is equivalent to injecting 6-60 ng into one *Xenopus* embryo (1.2 mm diameter). For whole embryos, 30-60 ng of morpholino was  
20 injected, and for blastomeres (animal-dorsal or animal-ventral blastomere to target the surface extoderm) 13-33 ng was injected.

Fig. 4 shows changes in neuronal markers after blastomere injection of Wise RNA and Wise antisense morpholino oligos (Figs. 4A-L). *In situ* hybridization with neural markers in

stage 16-21 *Xenopus* embryos following single blastomere injections of Wise RNA (Figs. 4B, 4E, 4H, and 4K) at the 8-cell stage and antisense morpholino oligos (Figs. 4C, 4F, 4I, and 4L) at the 4-cell stage are shown. The left panels (Figs. 4A, 4D, 4G, and 4J) indicate control embryos. In most embryos, lacZ (blue staining) was co-injected as a lineage tracer. Injected sides were to the left. Probes were Sox3 (Figs. 4A-4C), En2 (Figs. 4D-4F), Krox20 (Figs. 4G-4I), and Slug (Figs. 4J-4L). In Wise RNA injected embryos, the neural markers were generally displaced posteriorly. Ectopic induction of Krox20 and Slug can be seen in the forebrain region (Figs. 4H and 4K). In embryos injected with antisense morpholino oligos, these markers were unchanged.

Figs. 4M and 4N show the transverse sections at stage 16 after blastomere injection of either Wise RNA (Fig. 4M) or Wise antisense morpholino oligo (Fig. 4N). In Fig. 4M, the neural plate on the injected side was greatly expanded, which is revealed by Sox3 staining (dark blue, \*). Conversely, in the morpholino oligo-injected embryo (Fig. 4N), the surface ectoderm is thicker on the injected side (left, \*) in comparison to the right control side.

To further evaluate the effects of Wise on development of the neural tube, RNA or DNA was injected into specific blastomeres at 4-16 cell stages. When Wise RNA injections were targeted to presumptive neural regions, expression of pan-neural markers (Sox3, NCAM) confirmed an expansion of the neural plate (Figs. 4B and 4M). A-P specific markers (En2, Krox20, and Slug) were generally displaced laterally and posteriorly and were frequently expanded (Figs. 4E, 4H, and 4K).

Identical results were obtained using DNA constructs for injection, where Wise expression commenced at mid-blastula stages under the control of a cytoskeletal actin promoter. Together, these changes in morphology and neural patterning demonstrated that ectopic expression of Wise disturbed extension and closure of the developing neural tube.

The disruption of neural tube morphogenesis made it difficult to assay for posteriorizing influences in whole embryos. However, when Wise injected cells were targeted to the forebrain region, ectopic expression of Slug and Krox20 was observed (Figs. 4H and 4K). This indicated that anterior forebrain cells acquired a more posterior character in response to Wise.

5           Localized injection of the morpholino oligo resulted in embryos developing with thickened ectoderm, which contrasted with Wise RNA injections where embryos developed with a thickened neural plate (Figs. 4M and 4N). Neural markers, such as Sox3, En2, Krox20, and Slug, were not obviously affected at early neural stages (Figs. 4C, 4F, 4I, and 4L). This verifies that Wise and Wise mutants influence A-P patterning.

#### 10   **Example 6.**

Like Example 5, Wise RNA and morpholinos were injected into embryos. Injection of Wise RNA and morpholino oligos were observed to impact neural markers. Anterior defects after blastomere injection of Wise RNA or morpholino oligo were observed. Defects in anterior patterning, including a failure in eye formation, were observed at tailbud stages (Fig. 5H).

15       Furthermore, expression of the cement gland marker XCG was specifically down-regulated in cells expressing Wise (Figs. 5B and 5E). Conversely, when Wise injected cells were distributed more ventrally, the ectopic induction of the cement gland and XCG expression was observed (Fig. 5B). Therefore, ectopic expression of Wise altered aspects of A-P patterning in embryos, as well as animal caps.

20       Figs. 5A-5L shows *in situ* hybridization with the cement gland marker XCG at stage 16-20 (Figs. 5A-5C) and morphological phenotypes of cement gland at stage 26-40 (Figs. 5D-5F). Hybridization with the eye at stage 35-36 is shown at Figs. 5G-5I. The controls are shown in Figs. 5A, 5D, and 5G. Blue staining shows co-injected lacZ lineage tracer. Over-expression of



Wise resulted in formation of larger cement glands (Fig. 5C). Eye formation is consistently blocked by injection of both Wise RNA (Fig. 5H) and the morpholino oligo (Fig. 5I).

To analyze the endogenous role of Wise in embryogenesis, the *Xenopus* cognate was isolated and used to design morpholino antisense oligonucleotides, which would specifically  
5 interfere with translation of Wise RNA. *In vitro* translation of Wise was blocked by the morpholino oligo, whereas a control oligo had no effect (Fig. 5J). Fig. 5J shows *in vitro* translation of Wise in the presence of the Wise morpholino antisense oligo. Lane 1 shows translation of Wise protein without morpholino oligo. Lanes 2-7 show translation in the presence of the Wise morpholino oligo at concentrations of 0.1 nM, 1 nM, 10 nM, 100 nM, 1  
10  $\mu$ M, 10  $\mu$ M, respectively. Lane 8 shows translation in the presence of control morpholino oligo at the concentration of 10  $\mu$ M. Wise translation is partially blocked at concentration of 1  $\mu$ M, and completely blocked at 10  $\mu$ M.

When the morpholino oligo was injected into the whole embryo at the 1 cell stage, embryos developed cyclopic eyes (Figs. 5L-5N), and the trunk and tail were shortened in most  
15 cases (Figs. 5F and 5L). At later stages, morpholino-injected embryos showed defects in eye formation (Fig. 5I), which were rescued by co-injection of Wise RNA (Fig. 5K). Fig. 5K shows the rescue of the eye defect resulting from injection of the morpholino oligos by co-injection of Wise RNA.

Figs. 5L-5N are the phenotypes of embryos following injection of Wise morpholino  
20 oligos throughout the whole embryo. Fig. 5L shows the range of cyclopic eye and short trunk phenotypes induced by the oligos in comparison to the control embryo (left). Section of control (Fig. 5M) and morpholino-injected (Fig. 5N) embryos at the level of eye are shown. In the Wise morpholino-injected embryos, eyes are positioned very close to the neural tube.

These results suggest that the endogenous role of Wise is to mediate elongation of the trunk, morphogenesis of the ectoderm/neuroectoderm, and formation of the eye. The fact that both ectopic expression of Wise, and inhibiting its function by injection of the antisense morpholino oligo resulted in similar defects in eye formation, suggests that this process requires a precise level of signaling, mediated by Wise.

#### **Example 7.**

The present Example relates to the immunoprecipitation procedures previously discussed. To test protein secretion, RNA encoding the HA tagged version of Wise was synthesized and injected into *Xenopus* oocytes. This HA tagged Wise construct was confirmed to be functional by testing its ability to induce En2 in Noggin-injected animal caps. Fifteen oocytes were incubated in 96-well dish with 150  $\mu$ l of OR2 medium + 0.01% BSA for 2 days. Oocytes and the conditioned medium were collected separately and used for Western blotting with an anti-HA antibody (Boehringer). This construct was also transfected into COS cells and assayed for secretion by Western blotting.

For protein interaction studies, COS cells were transfected with DNA constructs encoding tagged versions of the proteins. Cells were harvested and proteins were extracted in 150 mM NaCl, 1% NP40, 0.5% Sodium Deoxycholate, 0.1% SDS, 50mM Tris-HCl (pH8), a cocktail of protease inhibitors (Complete, Boehringer), and 1 mM AEBSF at 4° C. Small aliquots were kept as cell extracts for checking expression of each protein. Primary antibodies against the epitope and Protein A-coupled beads were added to the extracts, incubated for 2 hours, and collected by centrifugation. Following several rounds of washing, pellets were re-suspended in loading buffer in the presence of SDS and subjected to electrophoresis and Western

blotting. The proteins were detected by using the epitope-specific antibodies and appropriate secondary antibodies conjugated to alkaline phosphatase.

#### Example 8.

The ability of Wise to interact with the Wnt pathway, and the fact that it is normally  
 5 expressed in a transient manner in the non-neural surface ectoderm, suggest that it might have a role in modulating Wnt signaling in this tissue (Fig. 3). A balance between Wnt and BMP signaling in the surface ectoderm and dorsal neural tube is important in modulating dorsal fates and the generation of neural crest cells. Furthermore, Wnts in the surface ectoderm influence patterning of the underlying somites and their derivatives. The distribution and timing of Wise  
 10 expression in the surface ectoderm, together with the result of morpholino experiments, suggest that it promotes precise levels of Wnt signaling to control some of these interactions.

Figs. 6A-6C show RT-PCR of Noggin treated animal caps assayed for En2 (en) induction. NCAM is used as a pan neural marker and Efla is a loading control. Fig. 6A shows the induction of En2 by Wnt8 or Wise RNA is blocked by dominant-negative (dn) Frizzled 8 ( $\Delta Fz8$ ). Noggin was added in an amount equal to (500 pg); Wnt8 was (50 pg); Wise was (1.2  
 15 ng); and  $\Delta Fz8$  (2 ng). In Fig. 6B, the following constituents were added: Noggin (500 pg); Wise (600 pg);  $\Delta Wnt8$  (200 pg);  $\Delta Dsh(dd1)$  (1.2 ng); GSK3 (500 pg); and LEFAN (200 pg). Fig. 6B shows the induction of En2 is blocked by dn-Wnt8 ( $\Delta Wnt8$ ), dn-dishevelled ( $\Delta Dsh(dd1)$ ), GSK3 and dn-Lef1 (LEFAN). Fig. 6C shows the induction of En2 requires signaling components of the  
 20 canonical Wnt pathway but not the planar cell polarity (PCP) pathway. Wise-mediated En2 induction was abolished by  $\Delta Dsh(dd1)$ , a dominant negative form of Dishevelled for both pathways, and  $\Delta Dsh(DIX)$ , which blocks the canonical pathway.  $\Delta Dsh(DEP)$  blocks the PCP

pathway but has no effect on Wise induction of En2.  $\Delta$ Dsh( $\Delta$ N) specifically activates the PCP pathway but fails to induce En2 in the absence of Wise, although full length d

Dishevelled (Dsh) is able to do so. In Fig. 6C, the following constituents were added: Noggin (500 pg); Wise (1.2 ng); Dsh (1 ng); and  $\Delta$ Dsh(d1),  $\Delta$ Dsh(DIX) and  $\Delta$ Dsh(DEP) (2.0  
5 ng). Figs. 6D-6G: TCF3 (300 pg); Wnt8 (25 pg); Wise (300 pg); and  $\beta$ -catenin (100 pg) were added in the listed amounts.

Figs. 6D-6G show staining for sub-cellular localization of endogenous  $\beta$ -catenin detected immunocytochemically in *Xenopus* animal caps following RNA injection of: D, TCF3; E, Wnt8+TCF3; F, Wise+TCF3; and G,  $\beta$ -catenin+TCF3. Wnt8 (E) and Wise (F) promoted  
10 accumulation of nuclear  $\beta$ -catenin.

Wise activated the Wnt signaling pathway in animal caps. Since Wnts and Wise both induced En2 expression in Noggin-injected animal caps, whether Wise required Wnt signaling for its activity was investigated. To test, Wise RNA was co-injected with either wild-type GSK3 $\beta$  or dominant negative (dn) versions of the canonical Wnt pathway components, Wnt8,  
15 Frizzled, Dishevelled or Lef1. All of these Wnt blocking reagents eliminated the ability of Wise to induce En2 in neuralized animal caps (Figs. 6A and 6B). The finding that dn-Wnt8 and dn-Frizzled8 blocked Wise activity implied that it may use the same receptor(s) as Wnt. With respect to the intracellular components, Dishevelled (Dsh) is an important branch point in Wnt signaling that separates the canonical nuclear pathway from a planar cell polarity (PCP) pathway.  
20 Different truncated dishevelled constructs were used to examine the roles of the different pathways in En2 induction. Both  $\Delta$ Dsh (dd1), which lacks a part of the PDZ domain necessary for both the canonical pathway and the PCP pathway, and  $\Delta$ Dsh (DIX), which is a specific dominant negative form for the canonical pathway, abolished En2 induction by Wise (Figs. 6B

and 6C). In contrast, both  $\Delta$ Dsh(DEP), which specifically blocks the PCP pathway, and  $\Delta$ Dsh ( $\Delta$ N) which constitutively activates the PCP pathway, had no effect on En2 induction (Fig. 6C). These results suggested that the domains of Dsh, critical for the canonical Wnt signaling pathway, are essential for Wise function.

## 5 **Example 9.**

This Example demonstrates that expression of Wise interferes with Wnt signaling. Although induction of En2 can be explained in terms of activation of Wnt signaling, the effects of injected Wise RNA on cement gland formation (Fig. 5B) resemble those seen when the Wnt pathway is inhibited. Therefore, it is possible that Wise also inhibits Wnt signaling. As such,  
10 Wise's ability to antagonize Wnt8 activity in axial induction was examined.

In particular, Figs. 7A-7C show the secondary axes induced by Wnt8 are blocked by Wise. Injection of Wnt8 RNA into a ventral vegetal blastomere of 4-8-cell stage embryos induced complete secondary axis formation (Fig. 7A). Co-injecting Wise blocked formation of Wnt8-induced secondary axis (Fig. 7B), similar to co-injection of a dominant negative  
15 Dishevelled,  $\Delta$ Dsh(DIX) (Fig. 7C).

Figs. 7A-7C show Wnt8 (5 pg); Wise (200 pg); and  $\Delta$ Dsh(DIX) (1 ng) that were added in the listed amounts. In Fig. 7D Wise (1 ng); Wnt8 (100 pg); Dsh (1 ng); and  $\beta$ -catenin (200 pg) were added in the listed amounts.

When Wnt8 RNA was injected into a ventral vegetal blastomere at 4-8 cell stages, it  
20 induced an ectopic secondary axis. Co-injection of Wise RNA completely blocked Wnt8-induced secondary axis. This inhibition was comparable to that mediated by a dominant negative form of Dsh (Fig. 7C).

Fig. 7D shows that Wise functions extracellularly to block induction of Siamois and Xnr3 by the Wnt pathway in ventral marginal zones. Wise blocks the ability of Wnt8 to induce Siamois and Xnr3, but it does not interfere with the ability of Dishevelled (Dsh) or  $\beta$ -catenin ( $\beta$ -cat) to induce these markers.

5        This inhibitory activity was examined at the molecular level in ventral marginal zone explants by assaying for Wnt-dependent induction of Xnr3 and Siamois, two immediate early response genes. In agreement with the axial duplication assays, the induction of Xnr3 and Siamois in ventral marginal zones by Wnt8 was blocked by the co-injection of Wise (Fig. 7D). However, Wise had no effect on the ability of injected intracellular components, such as  
10    Dishevelled and  $\beta$ -catenin to induce Xnr3 and Siamois (Fig. 7D). This suggests that Wise functions extracellularly to interfere with canonical Wnt signaling.

#### **Example 10.**

The inhibitory effect of Wise on the Wnt pathway was further examined by assaying secondary head induction dependent upon simultaneously blocking both BMP and Wnt  
15    signaling. When BMP signaling is blocked at the ventral marginal zone by a truncated BMP receptor (tBR), an incomplete secondary axis is formed (Fig. 7E). However, simultaneous inhibition of both BMP and Wnt signaling resulted in the formation of a complete secondary axis with eyes and cement glands. Co-injection of tBR and Wise induced a complete secondary axis (Fig. 7F), demonstrating that Wise blocked the Wnt pathway in this context.

20        Wise affected planar cell polarity. While the activation and inhibition properties of Wise in animal caps and embryos, described above, are dependent upon the canonical Wnt pathway, it is possible that Wise also influences the PCP pathway that branches at Dishevelled. Wnt11 is required for proper convergent extension movements of mesoderm during gastrulation in frogs

and fish, and this has been shown to be dependent upon the PCP pathway of Wnt signaling. Animal caps cultured in the presence of Activin form mesoderm and undergo convergent extension movements, which can be blocked by reagents that either elevate or decrease Wnt signaling. This implies that precise levels of Wnt signaling through the PCP pathway are essential for coordinated cell movements. Figs. 7E and 7F show that Wise acted as Wnt inhibitor and induced head attribute formation in an incomplete secondary axis system. When BMP signaling was blocked at the ventral marginal zone by injection of a truncated BMP receptor (tBR), an incomplete secondary axis was formed (Fig. 7E). Co-injection of tBR and Wise induced a complete secondary axis with eyes (arrows) and cement gland (Fig. 7F).

Figs. 7G-7I show how Wise blocks cell movements in Activin-treated animal caps. Control animal caps (Fig. 7G) undergo gastrulation-like movements in the presence of Activin (Fig. 7H). In Wise injected animal caps, elongation was blocked (Fig. 7I), but mesoderm induction occurred. In this animal cap assay, injection of Wise RNA blocked cell movements preventing elongation of animal caps, but had no effect on Activin-induced mesoderm formation (Figs. 7G-7I). This suggested that Wise influenced the Wnt-dependent PCP pathway, but whether activation or inhibition of the pathway resulted, cannot be distinguished. This effect on cell behavior in animal caps is consistent with and may explain the phenotypic effects observed in Wise-injected whole embryos. Wise perturbed the morphogenesis of the neural tube, which failed to close. It was thickened and shorter, and there was a lateral expansion and broadening of A-P markers. Many of these defects appear related to abnormal convergent extension movements during gastrulation. However, the fact that morpholino antisense oligo does not interfere the neural A-P markers (Fig. 4), and that Wise is not predominantly expressed at gastrula state (Fig. 2), both suggest that endogenous Wise is unlikely to be involved in

gastrulation movement. Instead, Wise has a potential to interfere with the Wnt-mediated PCP pathway.

**Example 11.**

The mechanisms of action were investigated as potential physical interactions of Wise, with Wnt family members or their putative co-receptors Frizzled (Hsieh et al., 1999) and LRP6 (Tamai et al., 2000) or Frizzled8 (Hsieh et al., 1999) with Wise conditioned medium, and assayed for interactions by immunoprecipitation (IP). In this assay, Wise bound to LRP6 and Frizzled 8, but not to Wnt8 (Fig. 8). Recent studies have shown that individual members of the Dickkopf (Dkk) family of secreted proteins can either antagonize or stimulate Wnt signaling through interaction with LRP6 (Brott and Sokol, 2002; Mao et al., 2001; Wu et al., 2000). Therefore, IP experiments were performed to determine if Wise shared common binding sites with Dkk1 or Wnt on LRP6. The extracellular domain of LRP6 contains four EGF repeats and Dkk1 interacts with repeats 3-4, while Wnt interactions seem to involve repeats 1-2 (Mao et al., 2001). It was found that Wise binds to LRP6 and a variant where EGF repeats 3 and 4 are deleted ( $\Delta$ E3-4), but not to one in which EGF repeats 1 and 2 are removed ( $\Delta$ E1-2)(Fig. 8A). Conversely, Dkk1 binds to LRP and  $\Delta$ E1-2, but not to  $\Delta$ E3-4 (Fig. 8A). These results showed that Wise shared the domain on LRP6 essential for interaction with Wnt and that Wise and Dkk1 modulate LRP6 activity by interacting through different domains. Wise and Wnt8 were tested to determine whether they could bind to LRP6 at the same time, or whether they compete for binding. As shown in Fig. 8C, Wise interferes with the binding of Wnt8 to LRP6. This suggested a mechanism, whereby Wise inhibits Wnt signaling by competing with Wnt8 for binding to LRP6 (Fig. 8D).



In conclusion, the results demonstrate that Wise influenced both the canonical and PCP pathways of the LRP/Wnt signaling cascade. The novel ability to both activate and inhibit Wnt signaling through actions of a single discrete regulatory molecule, places Wise in a unique position as a modulator of Wnt signaling.

## 5 Example 12.

In this Example, Sost inhibition of the Wnt pathway is described. It has been demonstrated that Wise acts to inhibit the Wnt pathway. The functional inhibition of Wnt was shown to be derived from the second exon of Wise, which encodes the cysteine knot. Since the cysteine knot of Sost is 70% homologous to that of Wise (Fig. 9), thus Sost's potential  
10 functioning in a similar fashion was explored. Sost RNA was either microinjected alone or in combination with other factors into *Xenopus* embryos and dorsal marginal zones were assayed for early immediate Wnt response genes, Siamois and Xnr3 (Fig. 11). It was found that, like Wise, Sost was able to inhibit the action of Wnt on Siamois and Xnr3 (Fig. 11). This Wnt inhibition by Sost was found to be working upstream from  $\beta$ -Catenin (Fig. 11). Like Wise, Sost  
15 was able to rescue secondary axis formation by Wnt (Fig. 11). However, unlike Wise, Sost was unable to completely restore a normal axis (Fig. 11).

Wise has also been shown to induce En2 at a distance in *Xenopus* Noggin animal cap assays. En2 expression at a distance is from an induction of Wnt gene activity. The conclusion was that Wise had induced, at a distance, more posterior neural markers in an anterior neuralized  
20 animal cap. Next it was analyzed whether Sost and Wise could be redundant by looking to see if Sost could also induce En2, like Wise. *Xenopus* embryos were either injected with Noggin and/or with Sost or Wise. We found that Wise injected animal caps induced En2 expression, however

Sost injected caps did not (Fig. 11). This unexpected finding led to further examination of these two genes.

### Example 13.

A Wise knockout mouse was made as detailed herein. A Neo-lacZ cassette, containing  
5 stop codons at the 3' end, was inserted into a Wise gDNA sequence isolated bacterial artificial  
chromosome (BAC) from a 129 strain of mouse by conventional cloning techniques. The mouse  
Wise DNA sequence is SEQ ID NO 1. A Sost knockout mouse can similarly be made. The  
mouse Sost sequence is SEQ ID NO 6. The Neo-lacZ cassette can be obtained from Stratagene  
(La Jolla, CA). The E. coli lacZ gene, when integrated into the mouse genome by standard  
10 cloning techniques, can be used as a reporter gene under the control of a given  
promoter/enhancer in a transgene expression cassette. The lacZ gene encodes  $\beta$ -galactosidase,  
which catalyzes the cleavage of lactose to form galactose and glucose. In the presence of X-gal  
chromogenic substrate,  $\beta$ -galactosidase converts the substrate into an insoluble blue dye,  
allowing identification of cells containing lacZ activity.

15 The 129 mouse strain, commonly utilized in creating "knockout" mice, was obtained  
from Jackson Laboratories, Bar Harbor, Maine. The Wise knockout mice produced lacked the  
presence of functional Wise polypeptide molecules. Sost knockout mice are predicted to lack  
functional Sost polypeptide molecules. Thus, these knockout mice may be referred to as  
functional mutants. In such mutant mice, protein translation is prematurely terminated.

20 A Neo-lacZ cassette, containing stop codons at the 3' end, was inserted into the first  
Exon of the Wise DNA, isolated BAC using the SmaI and EcoRI restriction sites. However, the  
Neo-lacZ cassette can also be inserted into a position within or adjacent to Exon 1 (SEQ ID NO  
127) and Exon 2 (SEQ ID NO 128) of Wise. The Wise-containing BAC preparation was

exposed to cleavage enzymes, such as SpeI and BamHI, which yielded homologous arms containing 5' UTR and 3' intron nucleic acid sequences. These nucleic acid sequences permitted homologous recombination with wild type DNA from 129 mouse-derived embryonic stem (ES) cells upon introduction of the BACs into ES cells by the electroporation method described in Example 32. The Neo-lacZ cassette contained one or more stop codons terminating translation of Wise polypeptide, leading to production of a truncated Wise polypeptide, which lacked the cysteine knot motif. The Wise cysteine knot region is significant because this region (1) is homologous to cysteine knot regions of Sost and other family members as described herein, and (2) binds to LRP.

After recombination, the ES cells were grown in the presence of G148 for neomycin selection. Neo-lacZ cassette-containing ES cells were neomycin-resistant and positively selected. There were three possible event outcomes occurring when the resultant ES cells were cultured in neomycin-containing media: First, Wise Neo-lacZ cassette-containing ES cells grew, indicating a successful homologous recombination event within the first Exon region of Wise, as predicted. Second, no recombination occurred, resulting in the lack of the presence of a protective Neo-gene in the ES cells and cell death. Third, recombination occurred outside the first Exon of Wise, conferring neomycin resistance and ES cell survival and growth.

To distinguish between the above first and third categories of recombination events in live neomycin-resistant ES cell cultures, genomic DNA (gDNA) extracted from ES cells was divided into two aliquots. One part was frozen (-20 deg. C) for further investigation, and the other part was digested *in vitro* with EcoR I for Southern Blot analysis. By using a 3' probe within Wise Exon 2, EcoR I digestion yielded either a 6.8 Kb fragment associated with a homologous recombination event, or a 9.0 Kb fragment associated with a random integration

event. Frozen cultures from those plates that exhibited homologous recombination event were thawed, expanded and further processed for creation of Wise mutant mice by micro-injection of these Wise Neo-lacZ cassette-containing ES cells into blastomeres as described hereinafter.

In the process of electroporation of mouse ES cells, linearized Wise nucleic acid sequences containing the Neo-lacZ cassette were inserted into the nuclei of ES cells for incorporation into the host ES cell DNA. Similarly, Sost nucleic acid sequences with the Neo-lacZ cassette can be inserted into the nuclei of ES cells for incorporation into other host ES cell DNA. The electroporation process steps were as follows. ES cells were obtained from removed blastocysts obtained from mouse uteri and grown on mitotically inactivated Mouse Embryonic Fibroblast (MEF) feeder layers. An ES cell frozen ampoule was thawed and transferred to a sterile dish containing MEFs as a feeder layer at a concentration of  $1 \times 10^6$  cells per 10 centimeter (cm) dish. ES cells were grown on the MEF feeder layer in ES media in T-150 flasks. ES cells were centrifuged and washed in transfection buffer ( $1 \times$  Hebs). ES cells were then placed in a sterile "flat pack" 1.8 mm gap cuvette (BTX order #485), and the cuvette was inserted between the safety stand contacts.

The power was switched to the on position with the BTX 600 or equivalent electroporator set to 500V/capacitance and resistance, 500 uF capacitance timing, 360 ohms R8 resistance timing, and charging voltage 185V. After pipetting the ES cells up and down with a 5 ml pipette, targeting construct DNA (40  $\mu$ g of clean linear DNA in  $1 \times$  TE @ 1  $\mu$ g/ $\mu$ l for each electroporation) was added to the ES cells in a microfuge tube. Cells were pipetted up and down gently with a Pasteur pipette. Cells were slowly added to the cuvette which was then placed into the electroporation chamber. The start button was pushed, and electroporation occurred. After completion, electroporated ES cells were removed from the cuvette and placed in 5.0 ml of fresh

ES medium in a centrifuge tube. 2 ml of transfected ES cells were added to each dish containing inactivated MEF feeder layers. Dishes were rocked slowly to evenly disperse cells and incubated. ES cells were fed on day 9 and 12 with selection medium, and clones became visible as small nests under an inverted microscope. Clones were picked on day 13 or 14 using a  
5 pipettor set between 30 and 50  $\mu$ l. Clones were each placed into one of 24 wells containing ES selection medium. On day 16 or 17, clones were frozen in ES freezing medium and stored at –70°C.

Each set of ES cells containing mutant Wise genes were injected into mouse embryos for creation of transgenic “knockout” mice. Such ES cells were microinjected into early mouse  
10 embryos (*i.e.*, blastocysts) which were then transferred to surrogate mothers for embryonic development. Targeted stem cells containing mutant Wise were placed in an injection chamber with expanded blastocysts. Stem cells were loaded into the injection needle and inserted into the blastocoel cavity of the recipient 129 or C57BL/6 embryo, then implanted into the uterus of a foster mother. Chimeric offspring were identified by coat color (*i.e.*, at 2 weeks) or other  
15 markers and confirmed by Southern blot analysis of tail biopsies (*i.e.*, at 3 weeks). Similarly, ES cells containing mutant Sost genes can be made and injected into ES cells to make Sost knockout mouse embryos.

The resulting pups (*i.e.*, chimeras) contained a (+) gene in some cells and a (-) gene in other cells. Chimeras were mated with normal mice. Pups were identified that carry one (+) and  
20 one (-) copy of the Wise gene, and these animals were mated with each other.

The mouse pups were then analyzed. About 25 percent of the pups were found to have inherited the (-) gene from both parents and completely lack the (+) or wild type gene. Homozygous (-) gene pups lacking the Wise wild type gene were termed “Wise knockout mice.”

Similarly, homozygous (-) gene pups lacking the Sost wild type gene can be made, and these are referred to as "Sost knockout mice." Wise knockout mice were then utilized for subsequent experiments to determine effects relating to bone mineral density, bone deposition, embryo implantation, hair development, tooth abnormalities, ophthalmic abnormalities. Sost knockout mice may similarly be made and utilized in phenotypic experiments.

**Example 14.**

A Sost knockout mouse can be made using the procedure of Example 13 above. Briefly, a Neo-lacZ cassette, containing stop codons, can be inserted into a Sost gDNA isolated BAC from a 129 mouse strain by conventional cloning techniques. The Sost-containing BAC preparation can be electroporated and allowed to undergo homologous recombination into ES cells and be exposed to selection. ES cells containing mutant Sost can be injected into mouse embryos for creation of transgenic Sost knockout mice as previously described.

**Example 15.**

In this Example, the Wise knockout mice, produced in Example 12, were used to investigate the effect of the absence of a functional Wise polypeptide molecule upon ophthalmic development. It was determined that ophthalmic abnormalities developed in these mutant mice. Immunodetection of Wise protein production in murine retinal regions was used to determine the efficacy of induced Wise mutation in the Wise mutant mice.

Polyclonal anti-Wise peptide antibody was prepared by rabbit immunization with Wise peptide antigens. Such antibodies were directed against the cysteine knot loop encoded by Exon 2 of Wise.

Zymed FITC-conjugated secondary polyclonal antibody directed against primary rabbit anti-Wise peptide antibody was also utilized in a histological sandwich immunoassay. Eye

mounts containing retinas or sections were stained with anti-Wise antibody and FITC-conjugated second antibody. In wild type mice, anti-Wise reactivity was detected as secreted Wise protein in the ganglion cell and optic fiber layers and in rods and cones. However, Wise mutant mice eyes lacked detectable anti-Wise peptide reactivity, indicating absence of Wise from tissues of these mutant mice.

The Wise mutant mice appeared to have lost the majority of the optic nerve fibers and had increased rod and cone layers in the retina (Fig. 12). These mice also exhibited abnormal retinal ganglion cells. Wise protein was found in the inner plexiform layer, ganglion cells and fibers, and in the rods and cone layer of a 2.5 month mouse retina (Fig. 12). Unlike Wise, Sost was found in the tissues adjacent to the neuroepithelium of the diencephalon at E18 dpc.

#### **Example 16.**

Wise mutants were analyzed to compare BMD in Wise mutants as compared to that in wild type mice. A Piximus instrument (Faxitron) was used to measure BMD, computed in whole mice by measurement of bone weight divided by area of bone measured.

The BMD in Wise mutants from the C57BL6 and 129 mouse strains was compared with that in wild type (wt) mice by the student t-test method. The resultant p value obtained for the BMD differences between C57BL6 vs. Wise mice was 0.0017. This indicates that BMD values increased in Wise mutant mice as compared to C57BL6 wt mice, with a significant difference between groups ( $p < 0.01$ ) observed. Increased BMD values were also observed in the 129 Wise mutant mice in comparison with 129 wt mice.

Related to this finding, Fig. 13 shows results of bone staining and BMD measurements. Fig. 13A and 13C depict hematoxylin and eosin (H&E) staining of cross-sections of bone tissue from 16 to 18 days post cortum (DPC) mice. Fig. 13B and 13D show the same bone regions as

Figs. 13A and 13C; however, Fig. 13B shows staining with S-35 radiolabel attached to Sost RNA probes, wherein Sost is located in osteoblasts in 16 to 18 DPC mice. Fig. 13D also shows staining with anti-Wise peptide primary antibody and FITC-conjugated secondary antibody, and localization of Wise in hypertrophic and prehypertrophic proliferating chondrocytes.

5            Fig. 13E and 13F show graphical depictions of bone density measurements and total bone weight measurements, respectively. Fig. 13E shows that observable significant differences in BMD measurements between Wise mutant and wild type mice occur at ages between 0 and 3 months. Wise mutant bone is higher in density than wt bone in this age range. At 4 months, there appears to be no significant difference between mutant and wt groups. Fig. 13F depicts  
10    total bone weight measurements. Note that at 2.5 months wt bone weight is 19.87, significantly different from the Wise bone weight of 24.67. Therefore, some of the increase in BMD found at 2.5 months can be attributed to increase bone weight and not necessarily an increased BMD. Consistent with data in Figs. 5E and 5F, it is concluded that during the 0 to 3 month period, bone deposition occurs. However, at the 4 month maturation stage, it is postulated that regulatory  
15    genes are switched on to remodel bone deposition and bone removal, wherein osteoclasts may be triggered to remove previously deposited bone.

          In summary, one tissue cell type that both Sost and Wise genes appear to affect in a similar fashion is the bone. Sost is expressed in osteoblasts. Sost may also be expressed in osteoclasts. In contrast, Wise is expressed in periosteum, and its protein is found on  
20    chondrocytes (proliferating, prehypertrophic and hypertrophic), but not in the growth plate (Fig. 5). Yet, both Sost and Wise genes display a similar phenotype of increased bone density, albeit potentially activated at different developmental stages. As such, Wise mutant mice have increased bone density during early prenatal bone development (under 4 months), and cease to



exhibit increased bone density once bone-modeling begins (4 months; Fig. 5). However, Sost mutations result in increased bone density during the subsequent developmental stage in which the adult bone remodeling process occurs.

**Example 17.**

Genetic regulation in tooth and jaw development was examined in wild type and Wise mutant mice as shown in Fig. 14. The mice were dissected, and the jaws were placed in a proteinase K solution (2x SSC, 0.2% SDS, 10mM EDTA, and 100ul of 10mg/ml proteinase K) overnight at 55°C. The next day the jaws were air-dried. A digital Faxitron was used for capturing X-ray images of the mouse jaw. The teeth were removed using tweezers.

Figs. 14A, 14D, and 14G show hematoxylin and eosin staining of a jaw cross-section. Figs. 14B, 14E, and 14H show S-35 RNA probe-labeled Sost staining. Figs. 14C, 14F, and 14I show S-35 RNA probe-labeled Wise staining. Generally, these figures show that Sost appears in odontoblasts and osteoblasts. In contrast, Wise is found in incisors, dental follicles, and hair follicles in the whisker pad.

The top sectional Figs. 14A, 14B, and 14C show a bilateral view of two molars with developing tooth buds. Fig. 14C shows that Wise labels layers of the dental follicle of molar teeth.

The middle sectional Figs. 14D, 14E, and 14F show a molar tooth bud at a higher magnification. Fig. 14E shows Sost staining in osteoblasts of the trabecular bone adjacent to the molar tooth. Visible staining of the odontoblasts occurs along the base of each molar. Fig. 14F shows Wise staining of dental follicle layers.

The bottom sectional Figs. 14G, 14H, and 14I show incisor tooth staining patterns. Fig. 14G shows the morphological features of two incisors, with the nasal cleft between them,

tongue, and hair follicles of the whisker pad. Fig. 14H shows Sost staining in osteoblasts of trabecular bone. Fig. 14I shows prominent Wise staining of incisors. Hair follicles and the whisker pad are also stained with Wise labeled RNA probes.

Figs. 14J and 14K show X-ray photographs of incisor teeth in the maxilla (upper jaw) regions of the wild type and Wise mutant mice, respectively, utilizing a 129 strain genetic background. The Wise mutant jaw, shown in Fig. 14K, possesses an additional incisor tooth (i') not present in the wt mouse shown in Fig. 14J. The additional tooth may originate from either an additional tooth bud or, alternatively, from a bifurcation of the original incisor.

Figs. 14L, 14M, 14N, and 14O show the patterning in molar teeth observed in wt (Figs. 14L and 14N) as compared to Wise mutant mice (Figs. 14M and 14O), against a C57BL6 genetic background (Figs. 14L and 14M) and 129 background (Figs. 14N and 14O). Fig. M shows an additional M1 molar in the Wise mutant mouse in comparison to the M1, M2, and M3 molars present in the wt mouse in Fig. 14L. Fig. 14O shows tooth abnormalities in the Wise mutant mouse. The M1 and M2 molar teeth are fused together. Moreover, there is a reversal of the order of molar bone patterning, wherein an M3/M2-1 pattern appears in the Wise mutant, in contrast to the wild type's M1/M2/M3 pattern. Occasionally, an additional M4 molar tooth appears in the Wise mutant.

It was observed that Wise mutant mice possessed tooth abnormalities. The incisors occurred in duplicate number in comparison with wt mice, and these teeth required weekly clipping from the weaning stage onwards. In addition, the molars also displayed abnormal patterning. The three molars were often found in reverse orientation and also showed fusion of M1 and M2. In contrast to Wise mice, Sost human mutations did not display these molar and incisor tooth phenotypic abnormalities, probably because of the differences in Sost and Wise

gene expression distributions in bone. Thus, Sost was expressed in the polarized odontoblasts and the surrounding osteoblasts. Wise, on the other hand, is expressed in the dental follicle surrounding the tooth bud and in the incisors. Thus, Sost and Wise were expressed in complementary cell types, wherein differing tooth and eye phenotypic expression patterns are anticipated and observed in Sost human mutations and Wise mutants.

#### **Example 18.**

Plasmid vectors containing Wise nucleic acid sequences were prepared for the purpose of producing Wise proteins and polypeptides. Sost vectors were similarly prepared for the purpose of producing Sost proteins and polypeptides. The expression vector, pET-28b (Novagen pET System Manual), was used for the expression of Wise and Sost, LRP5 and LRP6 sequences. This plasmid utilizes the phage T7 $\phi$ 10 gene promoter. This promoter is not recognized by E. coli DNA dependent RNA polymerase, and thus will not produce substantial levels of the polypeptide unless T7 RNA polymerase is present. Strain BL21 (DE3) contains a lysogenic  $\lambda$  phage that encodes the required polymerase under control of the lacUV5 promoter. A recombinant protein that was made was the intact Wise, Sost, LRP5 or LRP6 proteins. The Wise pET vector which was created by placing an EcoRI-HindIII fragment containing chick Wise cDNA into the pET28B vector which was then digested with EcoRI-HindIII. Extra amino acids 5' to Wise Start, ATG were removed, along with extra amino acids 3' to the Wise stop codon. The Sost pET vector was created by placing a BamHI-XhoI fragment containing mouse Sost cDNA into pET BamHI-XhoI. The amino acids from the 5' and 3' ends to the Sost coding region were removed using mutagenesis. The 3' amino acids were deleted and the missing ELENAY was inserted at the 3' end.

**Example 19.**

In this Example, the method used for protein production for Wise, Sost, LRP5, and LRP6 polypeptides in HEK293 mammalian cells is outlined briefly. PCS2+ Sost-FLAG, PCS2+ Wise-FLAG, or PCS2+ LRP6 IgG, PCS2+LRP5-Myc DNA was transfected into the HEK293 cells  
5 using FuGENE 6 Transfection Reagent (10 µg DNA/100 mm plate) (Roche Diagnostics Corp., Indianapolis, IN). The FuGENE reagent is a multi-component lipid-based transfection reagent that complexes with and transports DNA into the cell during transfection. Adherent cells were plated one day before transfection, and freshly passaged HEK293 suspension cells were prepared. FuGENE 6 reagent:DNA ratios of 3:2, 3:1 and 6:1 were used to transfect HEK293  
10 suspension cells.

After incubation, cell supernatants, containing the polypeptide of interest (Wise, Sost, LRP5, LRP6), were collected on days 1, 2, 3, and 4. Polypeptide-containing supernatants were concentrated by Amicon Ultra-15 column passage (20 ml to 500 µl). Some aliquots were frozen, and other aliquots were used in Western blot and immunoprecipitation quantitation and  
15 characterizations using standard methodologies. Mixtures of Wise and LRP5, Wise and LRP6, Sost and LRP5, and Sost and LRP6 were analyzed for binding by immunoprecipitation and Western blot analysis. See SuperSignal West Dura Western Blotting Kit (Pierce, Rockford, IL), Trans-Blot SD Semi-Dry Electrophoretic Transfer and Mini-PROTEAN 3 Electrophoresis (Bio-Rad Labs., Richmond, CA), Hybond – P PVDF Membrane for protein transfer (Amersham  
20 Pharmacia Biotech), Chroma Spin Columns (Clontech, Palo Alto, CA).

Immunoprecipitation was performed with anti-Wise antibody, anti-Myc, anti-Flag, and protein G sepharose (Sigma, St. Louis, MO) or protein A sepharose (Repligen). Briefly, transfected cell supernatants were prepared and 1-3 µg of antibody added. After incubation, 30

μl of protein G sepharose was added, incubated, and beads were centrifuged. Beads, containing antibody from supernatants as the immunoprecipitate, were washed in buffer, then submitted to SDS-PAGE analysis and Western Blot analysis. Alternatively, immobilized antibody was used in immunoprecipitation of proteins.

5           In Western Blots, electrophoresis was performed upon the cell supernatant material above. After wash, water rinse, and equilibration of the PVDF membrane in transfer buffer, papers were sandwiched as follows: pre-soaked thick paper, membrane, gel, pre-soaked thick paper. Power was turned to 10V to 15V for 30 min. After transfer of protein to the HyBond-P PVDF membrane, the membrane was incubated in blocking buffer, rinsed, and incubated with  
10   antibody solution. After wash, a secondary antibody was added, washed, then ECL-plus added. After exposure of X-ray film, patterns were read. As such, protein production in PCS2+ transfected HEK293 cells was performed to support purification and characterization of Wise, Sost, LRP5, and LRP6 polypeptides.

#### **Example 20.**

15           A method for the production of large quantities of Wise and Sost polypeptides is described. Bacteria cells transfected with either the Wise or Sost genes can be grown. E. coli strain DME558 is grown on LB agar plates at 37°C.

For P1 transduction, a P1 viral lysate of the E. coli strain DME558 is used to transduce a tetracycline resistance marker to strain BRE51 (Bremer, E., et al., FEMS Microbiol. Lett.  
20   33:173-178 (1986)) in which the entire OmpA gene is deleted (Silhavy, T. J., et al., Experiments with Gene Fusions, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. (1984)). Strain DME558, containing the tetracycline resistance marker in close proximity of the OmpA gene, is grown in LB medium until it reached a density of approximately 0.6 OD at 600 nm. One tenth of

a milliliter of 0.5 M  $\text{CaCl}_2$  is added to the 10 ml culture and 0.1 ml of a solution containing  $1 \times 10^9$  PFU of  $\text{P1}_{\text{vir}}$ .

The culture is incubated for 3 hours at 37° C. After this time, the bacterial cell density is visibly reduced. 0.5 ml of chloroform is added and the phage culture is stored at 4° C. Because  
5 typically 1-2% of the *E. coli* chromosome can be packaged in each phage, the number of phage generated covers the entire bacterial host chromosome, including the tetracycline resistance marker close to the *OmpA* gene.

Next, strain BRE51, which lacks the *OmpA* gene, can be grown in LB medium overnight at 37° C. The overnight culture is diluted 1:50 into fresh LB and grown for 2 hr. The cells are  
10 removed by centrifugation and resuspended in MC salts. 0.1 ml of the bacterial cells are mixed with 0.05 of the phage lysate described above and incubated for 20 min. at room temperature. Thereafter, an equal volume of 1 M sodium citrate is added and the bacterial cells are plated out onto LB plates containing 12.5  $\mu\text{g/ml}$  of tetracycline. The plates are incubated overnight at 37°  
15 C. Tetracycline resistant (12  $\mu\text{g/ml}$ ) transductants are screened for lack of *OmpA* protein expression by SDS-PAGE and Western Blot analysis, as described below. The bacteria resistant to the antibiotic possess the tetracycline resistance gene integrated into the chromosome very near where the *OmpA* gene had been deleted from this strain. One particular strain was designated BRE- $\text{T}^{\text{R}}$ .

A second round of phage production can be then carried out with the strain BRE- $\text{T}^{\text{R}}$ ,  
20 using the same method as described above. Representatives of this phage population contain both the tetracycline resistance gene and the *OmpA* deletion. These phage are then collected and stored. These phage are used to infect *E. coli* BL21(DE3). After infection, the bacteria contain

the tetracycline resistance marker. In addition, there is a high probability that the OmpA deletion is selected on the LB plates containing tetracycline.

Colonies of bacteria obtained from plates are grown up separately in LB medium and tested for the presence of the Wise and Sost protein and OmpA protein as judged by antibody reactivity on SDS-PAGE western blots.

The SDS-PAGE is a variation of Laemmli's method (Laemmli, U. K., Nature 227:680-685 (1970)) as described previously (Blake and Gotschlich, J. Exp. Med. 159:452-462 (1984)).

Electrophoretic transfer to Immobilon P (Millipore Corp. Bedford, Mass.) is performed according to the methods of Towbin et al. (Towbin, H., et al., Proc. Natl. Acad. Sci. USA

76:4350-4354 (1979)) with the exception that the paper is first wetted in methanol. The Western blots are probed with phosphatase conjugated reagents (Blake, M. S., et al., Analyt. Biochem. 136:175-179 (1984)).

#### **Example 21.**

The fusion constructs of Example 18 can be used to transform the expression strain BL21 (DE3)  $\Delta$ OmpA of Example 19. The transformation plates are cultured at 30°C. Colonies of both types are isolated from these plates and analyzed. It is generally found that virtually all transformants contained the desired plasmid DNA.

Various fusion-Wise clones are then analyzed for protein expression. The clones are induced and grown in LB media containing 0.4% glucose and 118  $\mu$ M carbenicillin instead of ampicillin with an aeration speed of 100 to 150 rpm and at about 30°C. The expression of the Wise protein is analyzed by loading 0.1 ml of the culture of total E. coli proteins on an 8-16% gradient SDS gel.

E. coli strain BL21 (DE3)  $\Delta$ OmpA [pNV-3] can be grown to mid-log phase (OD=0.6 at 600 nm) in Luria broth. Isopropyl thiogalactoside is then added (0.4 mM final) and the cells were grown an additional three hours at 30°C. The cells are then harvested and washed with several volumes of TEN buffer (50 mM Tris-HCl, 0.2 M NaCl, 10 mM EDTA, pH=8.0) and the cell  
5 paste stored frozen at -75°C.

For purification, about 3 grams of cells are thawed and suspended in 9 ml of TEN buffer. Lysozyme was added (Sigma, 0.25 mg/ml) deoxycholate (Sigma, 1.3 mg/ml) plus PMSF (Sigma, 10  $\mu$ g/ml) and the mixture was gently shaken for one hour at room temperature. During this time, the cells lyse and release DNA causing the solution to become viscous. DNase is then added  
10 (Sigma, 2  $\mu$ g/ml) and the solution again mixed for one hour at room temperature. The mixture is then centrifuged at 15 K rpm in an SA-600 rotor for 30 minutes and the supernatant discarded. The pellet is twice suspended in 10 ml of TEN buffer and the supernatants discarded. The pellet is suspended in 10 ml of 8 M urea (Pierce) in TEN buffer.

Alternatively, the pellet can be suspended in 10 ml of 6 M guanidine HCl (Sigma) in  
15 TEN buffer. The mixture is gently stirred to break up any clumps. The suspension is sonicated for 20 minutes or until an even suspension is achieved. 10 ml of a 10% aqueous solution of 3,14-ZWITTERGENT is added and the solution is thoroughly mixed. The solution is again sonicated for 10 minutes. Any residual insoluble material is removed by centrifugation.

This mixture is then applied to a 180.times.2.5 centimeter (cm) column of Sephacryl-300  
20 (Pharmacia) equilibrated in 100 mM Tris-HCl, 1 M NaCl, 10 mM EDTA, 20 mM CaCl<sub>2</sub>, 0.05% 3,14-ZWITTERGENT, pH=8.0. The flow rate is maintained at 1 ml/min. Fractions of 10 ml are collected. Three dimensional conformation was restored in Wise during the gel filtration. The absorbance (OD = 280 nm) of each fraction is measured and those fractions containing protein



are subjected to SDS gel electrophoresis assay for Wise. Those fractions containing Wise are pooled and stored at 4°C for 3 weeks. During the incubation at 4°C, a slow conformational change occurs. The Wise protein remained in solution without the elevated levels of salt. The pooled fractions are then dialyzed against 50 mM Tris-HCl, 200 mM NaCl, 10 mM EDTA, 0.05% 3,14-ZWITTERGENT, pH = 8.0. This material is applied to a 2.5x cm Fast Flow Q Pharmacia column equilibrated in the same buffer. Any unbound protein is eluted with starting buffer. A linear 0.2 to 2.0 M NaCl gradient is then applied to the column. The Wise elution profile can be characterized. Fractions are assayed by SDS-PAGE and the purest fractions pooled and dialyzed against TEN buffer containing 0.05% 3,14-ZWITTERGENT. Thus, cells transfected with the constructs can be isolated for Wise protein production. Similarly, Sost transfected cells can be isolated for Sost protein production.

#### **Example 22.**

The family tree associations of relatedness between Sost, Wise, and other cysteine knot proteins were analyzed. Sost and Wise cysteine knot protein sequences were analyzed using BLAST, and all significant sequences were isolated. The cysteine knots from all sequences were aligned using the software T-Coffee and then analyzed with Phylip bootstrap neighbor joining methods. To determine chromosomal locations, Wise and Sost DNA sequences were compared against sequences in the mouse and Ensembl database ([http://www.ensembl.org/Mus\\_musculus/blastview](http://www.ensembl.org/Mus_musculus/blastview)).

The BLAST program optionally filters out low-complexity regions from the search and assigns scores with well-defined statistical interpretation such that real matches of related sequences can be distinguished from random background hits. The default scoring matrix is BLOSUM62. The significance of each of the matches is given an Expect (E) score, defined as

the expected number of alignments between a random query sequence and a database of random sequences of the same “effective” length and number that will score as well.

A Wise cDNA, (SEQ ID NO 1) was isolated and submitted to NCBI for BLAST sequencing. The Wise cDNA was comprised of 618 nucleic acids, corresponding to 206 amino acids in the wild type polypeptide molecule. 743,070 sequences were searched in the database. From this search, it was determined that Wise and Sost were related. Both genes had two exons and an intron. Exon 2 for both genes was 400 bp long and possessed two cysteine domains that were 70% identical.

Fig. 9D shows the family tree relatedness between cysteine knot protein members Sost and Wise. In initial experiments, when the BLAST analysis was performed for Wise protein alone, only CCN family members (*e.g.*, Slit, Mucin) were obtained as related family members. When Sost alone was run, only DAN family members (*e.g.*, Caronte, Gremlin) were determined to be related. However, when Sost and Wise BLAST analyses were performed together, the family tree was that depicted in Fig. 9D. In this analysis of cysteine knot protein relatedness, it was noted that the DAN family had only one cysteine knot motif. In contrast, the CCN family and Slit and Mucin family possessed ten different protein motifs. Other family proteins had an additional cysteine knot moiety. G and P are conserved.

In Fig. 9D, the red dots indicate significant relatedness among cysteine knot proteins. Thus, Fig. 9D depicts the following family branch associations, wherein Sost and Wise are present in one branch. Nov, CTGF, Cyr61, and Cef10 are present in one closely related branch to Sost and Wise. Cerberus, Caronte, and Gremlin are in a second closely related branch. The aforementioned three branches are more remotely related to the following branches: the Muc2, Apomucpig, and Muc58 branch; the VWF branch, and the Slit 1, Slit2, Slit3, Muc5AC, and

Gastmuc branch. Numerical values in the tree in Fig. 9D indicate a measure of the significance of protein associations. The closer a number is to 100, the more significant the association. Numerical values of less than 50 indicates insignificant associations. Thus, the numerical value of 97 between Sost and Wise is highly significant.

5 **Example 23.**

An *in situ* protocol for detection of gene expression in Sost mutant mice was conducted. 3' untranslated regions of the Sost gene were obtained.

DNA from these 3' translated gene regions were linearized from the vector, then clipped at the 5' end. Subsequently, this sequence was transcribed to produce an antisense RNA  
10 molecule. The antisense RNA molecule was labeled with a deoxyguenin (DIG) substrate tag. The DIG-labeled RNA was then utilized to bind to an embryo's RNA.

In preparation for staining, a whole embryo was dehydrated and then bleached at the pigment stage. The next day, the embryo was washed and treated with detergent to induce permeability in subsequent staining. When the DIG-labeled RNA was incubated with RNA from  
15 an embryo, a purple-blue color was developed in whole embryo staining in the presence of alkaline phosphatase, NBT and BCIP. Using this procedure, Sost expression in whole embryo tissue was characterized.

**Example 24.**

A chick Wise pET28b vector was made. The Novagen pET28b(+) vectors used  
20 contained fl origin, N-terminal histidine, T7, and optional C-terminal histidine tags. Single-stranded sequencing was performed using the T7 terminator primer. An EcoR I-HinD III nucleic acid fragment was obtained from a chick Wise-containing pcDNA3.1-Myc-His vector for

insertion into the pET28b vector by established Novagen methods (Novagen, Madison, WI) described in various pET28b examples herein.

**Example 25.**

A mouse Sost pET28b vector was made. A Sost-V5 epitope-tagged version was utilized  
5 as a base construct for making the pET28b(+) construct. Subsequently, Sost was removed from  
the base construct using BamHI and XhoI enzymes and inserted into pET28b vectors according  
to Novagen methods as previously described. The Sost-containing preparation was expanded  
using the PCR method. Nucleic acids encoding thirteen excess amino acids were removed 5'  
from the start codon of the Sost nucleic acid sequence utilizing the Stratagene site-directed  
10 mutagenesis kit. Also removed were extra restriction enzyme sites adjacent to Xho or located at  
the 3' end of Sost. Naturally occurring nucleic acids in Sost encoding the last six ELENAY  
amino acids were added using mutagenesis.

**Example 26.**

In this Example, the chick Wise-FLAG sequence was inserted into the pCS2+ vector by  
15 procedures discussed in Example 19. The chick Wise sequence was placed in the pCS2+ vector  
using the EcoRI and SpeI/XbaI nucleases by cloning. The pCS2+ vector also contained T7, ClaI,  
BamHI, Sp6, and CMV sites. The chick Wise polypeptide was expressed and used to determine  
binding to LRP and BMPs.

**Example 27.**

20 This Example briefly describes the insertion of a mouse Sost sequence into the  
pcDNA3.1/V5-His-TOPO® vector. This TOPO® vector includes a CMV promoter, T7  
promoter/priming site, multiple cloning site, V5 epitope, polyhistidine tag, SV40 promoter,  
neomycin resistance gene, and ampicillin resistance gene. Mutagenesis permitted creation of the

wild type Sost-V5 vector using the following steps: (1) addition of the sequence encoding six ELENAY amino acids, and (2) addition of the EcoR I site to the 5' end of the Sost sequence.

**Example 28.**

Human wild type LRP6 and mutant LRP6- $\Delta$ 3,4 gene constructs in the pET28b vector  
5 were created and characterized. These gene constructs can then be utilized for the production of the corresponding mutant LRP6- $\Delta$ 3,4 protein molecule. After cloning the foregoing LRP6 gene construct into the pET28b vector by the method previously described in Example 3, the pET28b vector DNA was digested with BamHI and XhoI enzymes to yield the LRP6 sequence in soluble form for further characterization. This nucleic acid sequence was not linked to the  
10 transmembrane.

The EcoRV site was then mutated within the vector backbone using the Stratagene II QuikChange XL-Site Directed mutagenesis kit. This kit's procedure is used to make point mutations, amino acid substitutions, frame shift mutations, or insertion of single or multiple adjacent amino acids in Wise and Sost genes that encode polypeptides. The pET28 vector was  
15 digested with XhoI and EcoRV. The purified BamHI/EcoRV restriction enzyme fragment was cloned into pET28b. The first band corresponded to EGF1,2; and the second band corresponded to EGF3,4. The LRP6-derived EGF1,2 fragment was cloned into the pET28b vector containing BamHI and EcoRI sites by homologous recombination as previously described in Example 13. The Stratagene mutagenesis kit was used to obtain mutations in the pET28b vector containing  
20 the LRP6-derived EGF1,2 sequence. Subsequently, XhoI, NotI and EcoRV sites were introduced into the multiple cloning site of the pET28b vector. These sites permitted opening of the circular nucleic acid sequence with EcoRV and BamH endonucleases to allow insertion of

the LRP6-derived EGF1,2 fragment into the pET28b vector. LRP6- $\Delta$ 3,4 protein was then expressed from the pET28b vector.

**Example 29.**

This Example relates to the creation of the human LRP5 $\Delta$ 3,4 mutant-containing pET28b  
5 vector. Similarly, an LRP5  $\Delta$ -4 mutant-containing pET-28b vector can be made. A human LRP5  
nucleic acid sequence inserted into the CS2+ vector was obtained. The coding sequence for  
LRP5 in this vector runs from the EcoRI site to the XbaI site. The intact LRP5 was obtained by  
digestion with EcoR I and Xba I nucleases. As in Example 18, the purified BamHI/XbaI  
fragment was then digested with the XhoI enzyme to yield two bands, corresponding to LRP5  
10 EGF1,2 and EGF3,4 fragments. As previously, the LRP5 EGF1,2 sequence was inserted into the  
p28b vector containing EcoRI and XhoI sites. Site-directed mutagenesis was used to (1) remove  
the stop codon 5' to the actual start site and (2) delete extraneous nucleic acids located 5' to the  
start of the LRP sequence. The LRP  $\Delta$ 3-4 and LRP  $\Delta$ 3-4 vector subsequently can be used to  
independently transfect E. coli cells for production of LRP  $\Delta$ 3-4 and LRP  $\Delta$ 3-4 polypeptide  
15 molecules respectively.

**Example 30.**

This Example relates to the creation of the secreted LRP5-myc CS2+ vector. The human  
LRP5 containing pCS2 vector was obtained. Stratagen site-directed mutagenesis resulted in the  
following sequence modifications: (1) addition of the Myc tag upstream of the transmembrane  
20 domain, and (2) addition of XbaI and XhoI sites flanking the Myc tag region. Removal of the  
LRP5 sequence encoding the region that tethers the protein to the membrane was performed by  
digestion with XbaI nuclease. The resultant religated nucleic acid sequence encoded a secreted  
form of LRP5, lacking the tethered portion.

**Example 31.**

Hybridoma cell lines were prepared that can secrete monoclonal antibodies reactive with Wise wild type proteins, polypeptides, whole molecules, and fragments. The technology for producing monoclonal antibodies is well known. See generally E. A. Lerner, "How To Make A Hybridoma", Yale J. Biol. Med., 54, pp. 387-402 (1981); M. L. Gefter et al., "A Simple Method For Polyethylene Glycol-Promoted Hybridization Of Mouse Myeloma Cells", Somatic Cell Genet., 3, pp. 231-36 (1977). Briefly, murine X63AG8.653 myeloma cells are fused to lymphocytes isolated from spleens of mice immunized with a preparation comprising of Wise polypeptide (e.g., wild type Wise polypeptide SEQ ID NOS 45, 114-119), and the culture supernatants of the resulting hybridoma cells are screened as described herein for anti-Wise antibody binding activity. The myeloma cell line is HAT-sensitive, wherein growth in HAT medium selects for growth of HAT-resistant hybridoma cells.

To prepare Wise protein Immunogen, KLH-Immunogen is made. Wise Immunogen may be derived from Wise proteins or polypeptides. Representative Wise wild type proteins and polypeptides are SEQ ID NOs 45, 52, 104-106, and representative Wise mutant polypeptides are SEQ ID NOs 114-119. Each Balb/c mouse is immunized subcutaneously with 0.2 ml of a preparation containing about 100 µg of Wise polypeptide in PBS ("Immunogen") mixed 1:1 with Complete Freund's Adjuvant (CFA). Wise polypeptide was produced according to the method described in Examples 20-21. The Wise Immunogen polypeptide can be derived from wild type Wise molecules, as specifically described in SEQ ID NOs 45, 52, 104-106, 114-119. Shortened Wise polypeptide molecules are SEQ ID NOs 115-119. Three days after the final booster injection, mice are exsanguinated, antisera titrated, and isolated spleen cells are fused with the

non-secreting mouse myeloma cell line, SP2/0 Ag 14 (ATCC Designation CRL 8287).  
Thielmans, K., et al., J. Immunol. 133:495 (1984).

Prior to fusing, the resultant mouse antisera are titered to determine the concentration of anti-Wise antibodies made by each mouse. Pre-immune sera noted above are diluted in the same  
5 manner as the immune sera and used as controls. Microtiter wells are coated with 1.5 µg of BSA-Wise antigen prepared by incubating bovine serum albumin (BSA from Calbiochem, Catalog #12657, as described by Makita et al., J. Biol. Chem., 267(8), pp. 5133-5138 (1992). The antigen coated wells are sealed with Mylar sealing tape (Corning) and incubated overnight at 4°C. The microtiter plates are subsequently washed and blocked in a BSA-containing solution.  
10 After incubation, the microtiter plates are washed and 100 µl of a goat anti-mouse IgG (gamma chain specific) horseradish peroxidase-conjugated antibody (Sigma) is added to all wells and incubated. Ortho-phenylenediamine (OPD) Peroxidase Substrate (Sigma) is added to all wells and incubated. After the incubation period, the plates are read at 450 nm on a microtiter plate reader.

15 Anti-Wise antibodies are further characterized by their reactivity with the mouse bone, tooth, kidney, and other tissue, including but not limited to osteoblasts and osteoclasts. Monoclonal or polyclonal anti-Wise antibodies can be tested in an immunohistological assay using tissues, biochemically in an immunoprecipitation assay, and functionally in a Wnt pathway activation or inhibition assay. Briefly, anti-Wise antibodies are tested for reactivity with a panel  
20 of mouse sectioned or whole mount tissues and by immunofluorescence staining with fluorescein or rhodamine conjugated goat anti-mouse or rabbit immunoglobulin heavy or light chain reagents (TAGO, Burlingame, CA) using standard techniques. *See* Thielmans, K., et al., J. Immunol. 133:495 (1984) and Samoszuk, M.K., et al, Hybridoma 6:605 (1987). Other



colorimetric immunological reagents may be utilized in this immunohistological method. Alternatively, tissue-derived cell suspensions can be analyzed by either fluorescence microscopy or flow cytometry using a fluorescence activated cell sorter (Becton Dickinson FAXS 440, Mountain View, CA).

5           In a biochemical functional assay, anti-Wise antibody may be used to bind Wise protein or polypeptide, thereby inhibiting binding of Wise to LRP. Wise-FLAG and LRP-MYC reagents are made such that addition of anti-Wise antibody prevents Wise binding to LRP. In addition, anti-Wise antibody may immunoprecipitate Wise-FLAG, forming an antibody-antigen complex that is then detectable on Western blot analysis. Therefore, this assay may be used to  
10   detect anti-LRP antibody activity in functional inhibition of Wise-LRP binding. This functional assay is used as a screening tool to obtain antibodies, both monoclonal and polyclonal, which functionally bind to Wise protein *in vitro* and *in vivo* and prevent Wise binding to LRP. Similarly, anti-LRP antibodies may be screened. It is predicted that such therapeutic anti-Wise antibodies and anti-LRP antibodies can be used *in vitro* and *in vivo* to increase osteoblast number  
15   and bone mineral density and bone deposition.

          In a luciferase assay, anti-Wise antibody may function to activate the Wnt pathway. Here, Human293 cells are used wherein anti-Wise antibody binds to Wise and prevents such Wnt pathway inhibition.

          Upon completion of testing of anti-Wise antibodies in at least one of the above assays,  
20   those mouse sera and rhybridoma clones producing monoclonal antibodies that are reactive against Wise present in bone cells (osteoblasts, osteoclasts) can be selected for further expansion and processing. Goat antisera containing polyclonal antibodies reactive against Wise can also be produced.

Hybridoma production can be carried out by fusing the mouse spleen cells with the myeloma X63AG8.653 cell line by the procedure described in Harlow, E. and D. Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. The Sp-2/0 myeloma cell line may also be used. Briefly, spleen cells are mixed with HAT-sensitive X63AG8.653 myeloma cells and fused with polyethylene glycol (PEG) (e.g., 50% PEG 4000, Sigma Chemicals). Subsequent to fusion of spleen cells with the myeloma cell line, 1 drop of the 50 ml fusion mixture is added to each of 96 wells in 10 microwell cell culture plates (Corning). After culture of clones in selection media, hybridoma cultures are screened for antibody production to Wise antigen as follows:

Wise-polypeptide coated wells are prepared. Further, BSA is coated on wells following the same coating procedure as with BSA-Wise to detect any nonspecific binding. The antigen coated plates are used to screen cell culture supernates from each of the parental cultures. The parental supernates are added to one well of BSA-Wise-coated microtiter plate and to one well of BSA coated plate. The plates are incubated and washed. Goat anti-mouse IgG (gamma chain specific) horseradish peroxidase-conjugated antibody is added to each well. Parental cultures are identified that produce absorbance readings exceeding 0.3 O.D. on the BSA-Wise wells and no reactivity on the BSA coated wells. The latter parental cultures are expanded in culture in 24 well macrowell plates (Corning) and upon further supernatant/antibody evaluation, three parental cultures are re-cloned (secondary cloning). Following a procedure described in Harlow and Lane, supra, the parental cultures are diluted in RPMI 1640 culture medium containing 20% fetal bovine serum to give a cell density of 0.5-10 cells per well on wells that are precultured with splenocyte feeder cells.

After two weeks parental cell culture supernates are tested to determine the wells that are positive for monoclonal anti-Wise antibody activity using the screening procedure above. Positive wells are cloned and subcloned. Clonal cultures can be identified with high viability and producing the highest titer antibody to BSA-Wise in the aforementioned antibody screening assay. Secondary and tertiary subcloning of the latter is done to assure monoclonality and stability of the resultant clones. Comparative affinity analysis may be performed in accordance with Macdonald et al. (Macdonald, R. A. et al. 1988. Journal of Immunological Methods, 106:191-194). The cells from each culture are prepared in accordance with Harlow and Lane, supra, for frozen storage in ampoules in liquid nitrogen. Each single clone is expanded in culture and adapted to a protein-free medium (MaxiCell/Hybridoma-PF Medium, Cat. No. N10105, Atlanta Biologicals, Norcross, Ga.) for monoclonal antibody production. Thus, anti-Wise monoclonal antibodies are prepared that can be utilized in subsequently described bone deposition experiments.

Next, monoclonal antibodies from subclones can be tested against Wise wild type and mutant polypeptides for binding by direct ELISA and competition ELISA methods. For direct ELISA, BSA-Wise is coated on microtiter plates, the unbound sites are blocked by incubation with Assay Buffer (25 mM borate, pH 8.0, 150 mM NaCl, 0.01% EDTA and 1% BSA). The plate is washed 6X and increasing concentrations of monoclonal antibody (mAb) in Assay Buffer are added. After this incubation, the plate is again washed and incubated with alkaline-phosphates labeled goat anti-mouse antibodies (Cappel, Durham, N.C.) diluted 1:1000 in Assay Buffer. The unbound antibodies are removed by extensive washing and the bound antibodies are detected by addition of p-nitrophenylphosphate (PNPP). The optical density at 410 nm is recorded.

The competition ELISA can be performed by pre-coating microtiter plates with BSA-Wise wild type and mutant polypeptides and blocking with Assay Buffer. The plate is washed, and monoclonal anti-Wise antibody is added with increasing concentrations of the Wise wild type and mutant polypeptide antigen competitors, simultaneously incubating the mixture for 1 hr  
5 at 37° C. The unbound materials are removed by extensive washing and the bound mAb is detected with alkaline phosphatase labeled anti-mouse antibodies similar to the direct ELISA method above. All washes are in TBS-T wash solution; all incubations proceeded for 1 hr at 37° C. It is predicted that monoclonal antibodies directed against Wise immunogen will bind specifically to Wise wild type molecules. Such anti-Wise monoclonal antibodies, depending on  
10 their reactivity profiles, may or may not bind to Wise mutant molecules that do not bind to LRP.

Fab fragments of anti-Wise antibodies can be prepared. After purification of anti-Wise IgG antibody, Fab fragments are prepared by papain cleavage. Mercuripapain is pre-activated with 10mM cysteine in 1.25 MM EDTA for 15 min at 37° C, then added to the IgG antibody (5-10 mg/ml) at a 1:50 to 1:200 (w/w) ration of enzyme to antibody. The period of incubation at  
15 37° C ranged between 15 min to 5 hours to determine the optimum time of incubation for maximal Fab yield. Addition of iodacetamide (20 – 50 mM) stopped the cleavage process. Conditions are optimized by SDS-PAGE. analysis of resultant reaction products.

Thus, anti-Wise monoclonal antibodies and Fab “mini-antibody” fragments are prepared that can be utilized in subsequently described experiments below wherein such antibodies are  
20 delivered in liposomes to bone cells (*e.g.*, osteoblasts) for the purpose of increasing bone deposition and bone mineral density *in vitro* and *in vivo*. Anti-Wise Fab fragments are predicted to have greater anti-Wise inhibitory activity than whole anti-Wise antibody. Both anti-Wise

antibodies and their corresponding Fab fragments are expected to bind to Wise molecules in osteoblasts and prevent Wise molecule binding to LRP molecules (*e.g.*, LRP5, 6).

**Example 32.**

Hybridoma cell lines can be prepared that can secrete monoclonal antibodies reactive  
5 with Sost wild type proteins, polypeptides, whole molecules, and fragments according to the procedure described in Example 31 above. Briefly, murine myeloma cells are fused with murine splenic lymphocytes from mice immunized with Sost-derived antigen. Hybridomas making monoclonal antibodies reactive against Sost antigen are selected, grown, and monoclonal antibodies can then be screened with Sost antigen in EIA assays, histological tissue staining  
10 assays, immunoprecipitation assays, and functional assays as previously described. Fab fragments of anti-Sost antibodies can be prepared by standard papain and pepsin enzymatic digestion methods.

**Example 33.**

This Example relates to detection and analysis of the wild type, and also genetically  
15 modified, Wise cysteine knot regions in mammalian cells. Similarly, detection and analysis of the Sost cysteine knot region from wild type or genetically modified cells may be executed. In this procedure, murine C57BL/6 osteoblasts, producing Wise polypeptide are isolated. Other isolated or cultured mammalian cells can be used. Genetically modified Wise molecules can be made as presented in Example 18-21, wherein the stop codon in the Wise Neo-lacZ cassette,  
20 which is subsequently inserted into ES cells, encodes a truncated Exon 2 polypeptide product that comprises part of the cysteine knot region of Wise. After PCR amplification of these shortened Wise nucleic acid sequences by standard molecular biology cloning techniques, such

sequences are placed on Southern blots for gDNA and on Northern blots for mRNA species. J. Sambrook and D.W. Russell, Molecular Cloning: A Laboratory Manual, 3<sup>rd</sup> edition (2001).

More specifically, Wise gene nucleic acid fragment sequences for SEQ ID NOs 1 – 5 and 126 - 128 may be made and amplified by standard PCR technologies. These Wise nucleic acid sequences encode corresponding polypeptides. A smaller Wise gene DNA or RNA probe sequence corresponding to SEQ ID NO 1 can be synthesized (see SEQ ID Nos 136-140). Alternatively, site specific mutagenesis or *in vitro* transcription methods may be utilized. The DNA probe can then be labeled with P-32 cytosine (CTP). Alternatively, C-14, H-3, or other radiolabels or nonradioactive labels (*e.g.*, DIG) may be used. In addition, the RNA probe can be labeled with P-32 uracil. Once Wise DNA probes are labeled with P-32 cytosine, these radiolabeled probes may be hybridized to nucleic acids extracted from Wise-containing cells to characterize such Wise genes after Southern blot analysis. Similarly, radiolabeled Wise RNA probes may be hybridized to nucleic acids from Wise-containing cell extracts. It was observed that these Wise RNA fragments detected the presence of Wise nucleic acid sequences in the cell extracts.

#### **Example 34.**

Wise antigens to be prepared for immunization and to be used as standards in immunoassays include, but are not limited to, Wise wild type polypeptide whole molecule and polypeptide fragments. In addition, the corresponding Wise-derived nucleic acid molecules to the aforementioned polypeptide molecules were produced as antigens for immunizations and standards. Both Wise-derived polypeptide and nucleic acid antigens are prepared as previously described herein.

Goat and rabbit polyclonal antibodies and mouse monoclonal antibodies to the Wise-derived wild type and mutant polypeptide and nucleic acid molecules are prepared by methods that are known to those of skill in the art. E. Harlow and D. Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, New York, 1988. Similarly, goat and rabbit polyclonal antibodies and mouse monoclonal antibodies may be made to Sost-derived wild type and mutant polypeptides and nucleic acid molecules. The procedure for production of monoclonal antibodies to specific antigens has been described in detail herein. Once monoclonal and polyclonal antibodies to Wise-derived polypeptide and nucleic acid molecules have been made, they can be utilized in immunodiagnosics kit assays for the detection and quantitation of the Wise-derived molecules.

**Example 35.**

A Sost-specific monoclonal antibody can be made by the procedure as delineated in Examples 32 and 33. Sost-specific monoclonal antibodies may be made against Sost wild type and mutant proteins and polypeptides. These antibodies would inhibit the binding of Sost to LRPs.

**Example 36.**

This Example relates to the production of monoclonal antibody to the terminus region of LRP5 which binds to Wise protein. This LRP5 terminus region also binds to Sost protein. The anti-LRP5 antibody is predicted to inhibit binding of Wise to LRP5 and thereby result in phenotypic changes such as increased osteoblast number, increased bone mineral density and bone deposition, and tooth and ocular phenotypic changes. Similarly, the anti-LRP5 antibody is predicted to inhibit binding of Sost to LRP5, resulting in similar phenotypic changes.

LRP 5  $\Delta$ 3-4 mutants are made as described in Examples 28 and 29. Such LRP5  $\Delta$ 3-4 mutant nucleic acid sequences can be inserted into either p28b vectors as described in Examples 28 and 29, or Neo-lacZ cassettes (without stop codons) as described in Example 13. *E. coli* cells containing the p28b vector with the LRP5 mutation, and ES cells containing the Neo-lacZ cassette with the same mutation are cultured, lysed, and LRP5  $\Delta$ 3-4 purified.

Monoclonal antibody can be made to LRP5 by immunization of mice with LRP5 as described in Example 32, hybridization of LRP5 immunized mouse splenic lymphocytes with HAT-sensitive myeloma cells, and selection of HAT-resistant hybridoma cells secreting antibodies that bind LRP5. Once clones are identified that secrete antibody binding to LRP5, clones are further screened for failure to bind LRP5  $\Delta$ 3-4 in EIA and functional assays as described in Example 32. Such hybridoma clones that bind to wild type LRP5 molecules yet do not bind to LRP5  $\Delta$ 3-4 molecules are deemed to be putative anti-LRP5  $\Delta$ 3-4 region-epitope specific antibodies (LRP5  $\Delta$ 3-4). Photoreactive chemical conjugation of H3-radiolabeled antibody combining sites to the LRP5 molecule can verify this antibody-specific attachment to the terminal amino acid sequence of LRP5.

#### **Example 37.**

This Example relates to the production of monoclonal antibody to the terminus region of LRP6 which binds to Wise protein. The anti-LRP6 antibody is predicted to inhibit binding of Wise to LRP6 and thereby result in phenotypic changes such as increased osteoblast number, increased bone mineral density and bone deposition, and tooth and ocular phenotypic changes. Similarly, the anti-LRP6 antibody is predicted to inhibit binding of Sost to LRP6, resulting in similar phenotypic changes.



LRP 6  $\Delta$ 3-4 mutants are made as described in Examples 28-29. Such LRP 6  $\Delta$ 3-4 mutant nucleic acid sequences can be inserted into either p28b vectors as described in Examples 28-29, or Neo-lacZ cassettes (without stop codons) as described in Examples 13. E. coli cells containing the p28b vector with the LRP6 mutation, and ES cells containing the Neo-lacZ  
5 cassette with the same mutation are cultured, lysed, and LRP6  $\Delta$ 3-4 purified.

Monoclonal antibody can be made to LRP6 by immunization of mice with LRP6 as described in Example 32, hybridization of LRP6 immunized mouse splenic lymphocytes with HAT-sensitive myeloma cells, and selection of HAT-resistant hybridoma cells secreting antibodies that bind LRP6. Once clones are identified that secrete antibody binding to LRP6,  
10 clones are further screened for failure to bind LRP 6  $\Delta$ 3-4 in EIA and functional assays as described in Example 32. Such hybridoma clones that bind to wild type LRP6 molecules yet do not bind to LRP 6  $\Delta$ 3-4 molecules are deemed to be putative anti-LRP6  $\Delta$ 3-4 region-epitope specific antibodies (LRP6  $\Delta$ 3-4). Photoreactive chemical conjugation of H3-radiolabeled antibody combining sites to the LRP6 molecule can verify this antibody-specific attachment to  
15 the terminal amino acid sequence of LRP6.

#### **Example 38.**

This Example relates to the production of biotinylated liposomes which are then linked to monoclonal antibodies specific for osteoblasts through an avidin linkage. These anti-osteoblast antibody-armed liposomes can be utilized to deliver encapsulated anti-Wise antibody to  
20 osteoblasts. Similarly, encapsulated anti-Sost antibody may be made and delivered to osteoblasts. Liposomes may be armed with anti-osteoblast (anti-OB) antibodies that react with either mouse or human osteoblasts as described herein. Delivery of anti-Wise antibodies to

osteoblasts using encapsulated liposomes is anticipated to result in increased osteoblast growth and proliferation with concomitant increased bone deposition.

Biotinylated phospholipids are initially prepared. Biotinylated phospholipids are prepared by dissolving phosphatidylethanolamine (PE, 5.1 mg) or phosphatidylserine (PS, 3.9 mg) in a solution (170  $\mu$ l for PE; 130  $\mu$ l for PS) of chloroform-methanol (2:1) with biotinyl N-hydroxysuccinimide ester (BNHS, 3.3. mg) (Sigma Chemicals, St. Louis, MO). 10  $\mu$ l is added of a chloroform solution containing 15% (v/v) triethylamine. After a two hour incubation of the reaction mixture at ambient room temperature (18° C), the crude mixture is stored at -70° C.

The crude biotinylatedlipid is then purified by high-performance liquid chromatography (HPLC) using a Waters system (Waters Associates, Milford, MA) with two solvent delivery units (M-45 and Model 510) and a Model 680 gradient controller. Separations are performed using a stainless steel column (250 x 4.6 mm i.d.) packed with 5  $\mu$ m Lichrosorb Si-100 silica (Merck, Darmstadt, Germany) at room temperature with a flow rate of 1 ml/min. After a first wash with solvent A (n-hexane/2-propanol/sater in a ratio of 60:80:14, v/v/v), Solvent B (n-hexane/2-propanol/water 60:80:7, v/v/v) is added until a new baseline is stabilized.

10  $\mu$ l of the crude biotinylated lipid starting reaction mixture containing 390 nmol lipid is applied to the HPLC column using a Hamilton syringe, and the elution is monitored utilizing an M-441 UV detector (214 nm). The column is eluted for 5 min with solvent A, then with a 20 min linear gradient between 0 and 100% solvent B in A. Solvent B is then passed over the column until a stable baseline is obtained.

The average retention times of BPE and BPS are 20.7 min (17-22) and 27.1 min (26-28), respectively. The HPLC peaks are collected in a Gilson Microfractionator, and the eluted

material is pooled. The solvent is then evaporated under a stream of nitrogen, and the biotinylated lipid is stored at  $-70^{\circ}\text{C}$ .

Both the initial crude reaction mixture and the HPLC-purified BPE and BPS fractions are analyzed by thin-layer chromatography (TLC) in silica gel-coated plates (Riedel-de Haen, Germany). For BPE plates, a chloroform/methanol/water (80:25:2) solution is used; and for BPS plates, a chloroform/methanol/acetic acid (30:4:3) solution is used. Phospholipid visualization occurs through one of three methods: (1) exposure to iodine vapors, (2) a biotin-specific spray (dimethylaminocinnamaldehyde) *See* D.B. McCormick and J.A. Roth *Methods in Enzymology* 148A: 383 (1987), or (3) a phosphate-specific spray. *See* V.E. Vaskovsky and E.Y. Kostetsky, *J. Lipid Res.* 9: 396 (1968). All three staining methods reveal that BPE has an  $R_f = 0.65$ , and BPS has an  $R_f = 0.55$ .

Biotinylated liposomes are then prepared. Biotinylated phospholipids (BPE or BPS) are dissolved in chloroform/methanol (2:1) and molar equivalents of each corresponding lipid (BPE or BPS) are added to 12 mm x 75 mm glass tubes to yield the final percentage of biotinylated lipid desired (*e.g.*, 5, 10, 20%). Concentrations of 0.01 to 1 mol% of total lipid are achieved.

To prepare liposomes, the biotinylated lipid/native lipid mixture (*e.g.*, 2  $\mu\text{mol}$  of the stock lipid mixture in chloroform/methanol) is evaporated to dryness under a stream of nitrogen and then placed in a vacuum dessicator overnight. The lipid is resuspended by syringe injection (*e.g.*, 50  $\mu\text{l}$  lipid in chloroform/methanol into 1.0 ml PBS) in a final concentration of 1 mg/ml in PBS, pH 7.2-7.4, then sonicated under nitrogen in an ice-cooled chamber for 10 min in a Branson Sonifier Model 130. The resulting suspension is centrifuged at 10,000 rpm for 20 min, and the biotinylated liposomes in the supernatant fraction used within 24 hours after preparation.

To encapsulate anti-Wise antibodies, the biotinylated lipid/native mixture is resuspended by injection (*e.g.*, 50  $\mu$ l lipid in chloroform/methanol into 1.0 ml PBS) into an anti-Wise antibody-containing PBS solution. After sonication and centrifugation at 10,000 rpm for 20 minutes, anti-Wise antibody-biotinylated liposomes are purified by one of the following  
5 procedures: (1) in one preferred procedure, liposome preparations are centrifuged at 13,000 x g in a microcentrifuge; pelleted liposomes are washed with PBS, and pelleted liposome fractions are resuspended in PBS buffer for use; (2) in another method, liposome preparations are passed over a Sephadex 200 column (Pharmacia, Piscataway, NJ) in PBS. The liposomes are eluted in the PBS void volume, with free protein and contaminants appearing in subsequent collection.

10 Once the liposomes are prepared, Fab fragments of anti-osteoblast cell (anti-OB) antibodies must be prepared. Rat anti-mouse Thy-1 monoclonal antibody and mouse anti-human Thy-1 monoclonal antibody are obtained from Pharmingen (San Diego, CA). Thy 1 is known to be an expressed surface antigen on osteoblast cells. X-D Chen, et al., Thy-1 Antigen Expression by Cells in the Osteoblast Lineage, J. Bone & Mineral Research 14(3): 362-375 (1999). Other  
15 suitable osteoblast-reactive antibodies have been described. *See, e.g.*, Aubin, J.E. et al. Monoclonal antibodies as Tools for Studying the Osteoblast Lineage, Microsc Res Tech 33:128-140; Bruder SP et al. (1996) Monoclonal Antibodies Selective for Human Osteogenic Cell Surface Antigens, Bone 21:225-235. After purification of anti-OB IgG antibody, Fab fragments are prepared by papain cleavage. Mercuripapain is pre-activated with 10mM cysteine in 1.25  
20 mM EDTA for 15 minutes at 37° C, then added to the IgG antibody (5-10 mg/ml) at a 1:50 to 1:200 w/w) ratio of enzyme to antibody. The period of incubation at 37° C. ranged between 15 minutes to 5 hours to determine the optimum time of incubation for maximal Fab yield.

Addition of iodoacetamide (20-50 mM) stopped the cleavage process. Conditions are optimized by SDS-PAGE analysis of resultant reaction products.

Biotinylated Fab fragments of anti-OB antibodies are obtained by using an N-hydroxysuccinimidobiotin (NHS-Biotin, Sigma Chemical, St. Louis, MO). In this method, 2 mg  
5 of Fab fragments are dissolved in 1 ml of sodium phosphate buffer (PBS), pH 7.5-8.5, in a 16 x 125 mm test tube. Immediately before use, 1 mg of NHS-Biotin is dissolved in 1 ml dimethylformamide (DMF). 75  $\mu$ l of the dissolved NHS-Biotin is added to the Fab containing test tube. The tube is incubated on ice (4° C) for 2 hours. The unreacted biotin may be removed by dialysis (*e.g.*, Slide-A-Lyzer Dialysis Cassette) or with a D-Salting Column (Pierce Chemical,  
10 Rockford, IL). Alternative, unreacted biotin may be removed by centrifugation of the product at 1000 x g for 15-30 minutes using a microconcentrator. After centrifugation, the sample is diluted in 0.1 M sodium phosphate, pH 7.0. The process can then be repeated twice more. The biotinylated protein may be stored at 4° C in 0.05% sodium azide prior to use.

Finally, Fab-anti-Wise liposomes utilizing biotinylated Fab molecules, biotinylated  
15 liposomes and avidin are prepared. The biotinylated Fab fragments in PBS are mixed with a twenty-fold molar excess of egg white avidin (Vector labs, Burlingame, CA; Sigma Chemical, St. Louis, MO), incubated overnight at 4° C. The excess avidin is removed by passage of the mixture over anti-human light chain affinity columns (*e.g.*, Pharmacia Sepharose 4B). Fab-biotin-avidin molecules are eluted with citrate buffer, pH-4.0, then pooled fractions are dialyzed  
20 against PBS, pH=7.0. A suspension of biotinylated anti-Wise antibody-containing liposomes is mixed with Fab-biotin-avidin solutions in PBS to yield avidin to free biotin ratios on the liposome surfaces of approximately 2:1, 5:1, 10:1, and 20:1 molar ratios. After incubation overnight at 4° C on a rotational shaker, liposomes are passed through a Pharmacia Sephadex G-

200 column. The Fab-anti-Wise liposomes are collected in the void volume and resuspended in PBS.

Alternatively, biotinylated anti-Wise antibody-containing liposomes are mixed with a twenty-fold molar excess of streptavidin, incubated overnight at 4° C, then biotinylated-avidin liposomes are passed over the anti-human light chain affinity column. Biotinylated-avidin anti-Wise liposomes are eluted with a citrate buffer, pH = 4.0, then pooled fractions are dialyzed against PBS, pH=7.0. After dialysis, biotinylated-avidin liposomes are mixed with biotinylated Fab fragments in PBS in the above approximate molar ratios. Similarly, after incubation overnight at 4° C on a rotational shaker, liposomes are passed through a Pharmacia Sephadex G-200 column. The Fab-Anti-Wise antibody liposomes are collected in the void volume and resuspended in PBS.

### Example 39.

The present Example relates to *in vitro* treatment of mouse bone cells (*e.g.*, osteoblasts and osteoclasts) by anti-Wise-specific Fab liposomes armed with anti-osteoblast antibody as prepared in Example 40. The anti-Wise antibody may have specificity for Wise whole molecule or polypeptides. Similarly, anti-Sost antibody may be encapsulated in liposomes to obtain osteoblast phenotypic effects *in vitro*. First, murine bone cells are purified by fluorescence activated cell sorting (FACS) using anti-bone marker antibodies. In addition, mouse bone cell osteoblasts can be prepared essentially as described by Takahashi et al., 1988 Endocrinology 123:2600-2602; and by Tanaka et al., 1992 J. Bone Min Res. 7:S307, which are incorporated by reference herein. These bone cells are liquid nitrogen-cryopreserved in ampoules.

Bone cells are separated by fluorescence activated cell sorting (FACS) utilizing the FACStar-PLUS flow cytometer (Becton Dickinson) equipped with two 5-watt argon ion lasers

and a tunable dye laser interfaced with a Digital Equipment Corporation Vas Station-4000/90 computer and data collection/analysis software. Bone cells are prepared by suspension in MACS (magnetic sorting) buffer with fluorescein-conjugated antibody directed against mouse osteoblasts (DAKO, Carpenteria, CA) in a tube and vortexed. After incubation for 30 minutes at 4° C, cells are washed 3 – 5 times in MACS buffer, then centrifuged at 400 x g for 5 minutes at 4° C. Cells are placed in MACS buffer at 4° C for separation in the FACStar flow cytometer. Mouse bone cells are separated on the basis of the fluorescence and size. Aliquots of purified murine osteoblasts and osteoclasts cells are tested for reactivity with anti-Wise antibodies in a fluorescence sandwich immunoassay with murine monoclonal anti-Wise antibody made according to the method of Example 32 and fluorescein-conjugated goat anti-mouse IgG antibody (H & L) (DAKO, Carpenteria, CA). Cells are stained for viability (>90%) by Trypan blue staining.

Subsequent to viable bone cell isolation above, bone cells (primarily osteoblasts or osteoclasts) are incubated *in vitro* with anti-Wise antibody-containing liposomes. An aliquot of anti-Wise-liposome-bone cells are then lysed. Polypeptide molecules of the elysate are separated and characterized by SDS gel electrophoresis and Western blot analysis. Reduction of Wise binding to LRP in the presence of anti-Wise antibody in bone cells can be measured.

It is predicted that anti-Wise antibody and anti-Wise Fab fragment molecules will both inhibit binding of wild type Wise to LRP5 in osteoblasts *in vitro*. In contrast, anti-Wise antibodies and fragments should not bind to osteoclasts, nor assert an effect on osteoclast activity (*e.g.*, bone resorption). Correspondingly, based in part upon results described in Example 16 herein, it is expected that anti-Wise inhibition of Wise binding to LRP5 will result in increased growth and number of osteoblasts. Such increase in osteoblast number has previously

been associated with concomitant increases in bone deposition and bone mineral density *in vivo*, as described in Example 16. Thus, treatment with anti-Wise liposomes is predicted to result in increased bone deposition and bone mineral density in *in vivo* mouse studies.

**Example 40.**

5           The present Example relates to *in vivo* treatment of nude mice implanted with murine bone cells (*e.g.*, osteoblasts, osteoclasts) with anti-Wise antibody-containing liposomes. Congenitally athymic nude mice containing murine bone fragment implants can be used as a test system for assessing the anti-Wise antibody-containing liposomes on murine bone cell growth *in vivo* according to the procedure described herein.

10           Congenitally athymic homozygous CD-1 female nude scid/scid mice (SCID, Charles River Laboratories, Wilmington, MA) are housed in sterile cages, treated with antibiotics and give autoclaved food and water. At approximately 6 – 8 weeks old, SCID mice can be injected subcutaneously with cut fragments of femurs and tibias of allotypically different murine fetuses or immature pups. Balb/c mice can be used as bone donors. Intraperitoneal injection of mice  
15 with bone fragment marrow implants is an alternative rout of administration. These mice may now be referred to as “SCID-bone mice.” Murine implanted bone fragment marrow grafts are allowed to “take” for approximately 6 – 8 weeks prior to injection with anti-Wise antibodies. Fetal donor bone cell suspensions are analyzed for murine allotypic markers.

20           As previously described herein, Fab anti-Wise antibody-containing liposomes can be prepared.  $0.5 - 5.0 \times 10^6$  bone osteoblast cells are suspended in 20 ml of complete RPMI-1640 medium and injected with a Hamilton microliter syringe into each of the 6 – 8 week old murine bone marrow grafts of the SCID-bone mice. In the first experiment, Fab anti-Wise antibody liposomes (200:1; 100:1, 50:1 liposome:cell ratios) can be mixed together with bone cells prior



to injection *in vivo*. In the second experiment, bone cells can be injected into the bone fragment marrow grafts, then anti-Wise antibody-containing anti-osteoblast antibody-armed liposomes (200:1; 100:1; 50:1 liposome:cell ratios) can be injected by several routes: (1) directly into the murine bone marrow, 4, 6, and 24 hr after murine bone fragment implantation; and (2) intravenously in the mouse tail vein at 0, 4, 6, and 25 hr after murine fragment implantation. Alternatively, and perhaps preferably, anti-Wise antibody-liposomes may be mixed with osteoblasts or osteoclasts prior to placement in operably contact with the implanted bone fragment. Controls would include anti-Wise antibody-containing liposomes wherein the attached arming antibody lacks osteoblast-binding specificity, and liposomes lacking anti-Wise antibody.

The effect of anti-Wise antibody-liposome treatment on bone cells can then be assessed by the following procedure. Growth of bone cells (*i.e.*, osteoblasts, osteoclasts) can be analyzed by examining cells harvested from SCID-bone mouse bone fragment marrow implants at 1, 2, 4, 8, 16, and 32 weeks after anti-Wise antibody-liposome injection. Harvested cells can be analyzed by flow cytometry in the FACScan system after suspension in complete RPMI-1640 medium, washing in RPMI, lysing of red blood cells with ammonium chloride, and staining with immunofluorescent reagents. Immunofluorescence sandwich markers including fluorescein- or rhodamine-conjugated goat anti-mouse IgG (H & L) antibody can be used in conjunction with murine monoclonal anti-Wise anti-body. Histological sections of bone, bone marrow, spleen, lymph node, lung and other tissue can also be prepared 1, 2, 3, and 4 months after bone cell implantation, sectioned, and stained with immunofluorescence reagents described above or with hematoxylin and eosin-stained formalin-fixed and paraffin-embedded specimens compared with specimens from untreated, control SCID-bone mice in which no osteoblast or osteoclast cells are

injected. Significantly, SCID-bone mice may be analyzed for treatment with anti-Wise antibody-liposomes to determine efficacy of such liposomes to increase in growth and number of osteoblasts which is expected to result in increased bone deposition in this *in vivo* SCID nude mouse model system. Moreover, SCID-bone mice may be used to assess anti-human Wise antibody treatment effects utilizing xenogeneic human bone fragment transfers into such SCID-bone mice as described herein.

**Example 41.**

This Example relates to injection of anti-Wise antibodies into the pups of the C57BL/6 mouse strain to determine their positive effects on Wise-regulated phenotypes. Alternatively, the 129 mouse strain may be used. Monoclonal and polyclonal anti-Wise antibodies specific for wild type Wise polypeptide molecules were made as described in Example 31 above. The antibody can be directed to the cysteine knot-containing region of Wise. Similarly, anti-Sost antibodies may be injected into mouse pups to determine phenotypic and therapeutic changes.

In this procedure, C57BL/6 mouse pups are injected with therapeutic doses of anti-Wise antibody in a pharmaceutical carrier such as sterile endotoxin-free phosphate buffered saline (PBS) at 2, 4, 6, 8, 10, 12, 14, 16, 18, and 20 days post partum. Alternatively, anti-Wise antibody Fab fragments may be used in a suitable pharmaceutical carrier medium. Bone mineral density of injected mice is compared to that of uninjected control mice as described in Example 16. It is anticipated that anti-Wise antibody treatment will result in increased bone mineral density and increased bone deposition in injected mice as compared to controls.

It is also predicted that anti-Wise antibody treatment will result in phenotypic changes in eyes and teeth as described in Wise mutant mice in Examples 15 and 17 above. Thus, anti-Wise antibody injected mice are expected to exhibit loss of optic nerve fibers and increased rod and

cone layers in the retina as shown in Example 15 in Wise mutant mice. Anti-Wise antibody injected mice are predicted to manifest molar and incisor tooth abnormalities similar to those of Wise mutant mice as demonstrated in Example 17. An additional incisor tooth phenotype not present in the wild type mouse may be observed. In addition, anti-Wise antibody injected mice  
5 may show an additional M1 molar tooth, with an additional associated root. Anti-Wise antibody injected mice may also exhibit reverse orientation patterning of molar teeth, with possible fusion of M1 and M2 teeth.

**Example 42.**

In this Example, kit components for detection and quantitation of Wise wild type and  
10 mutant polypeptides and fragments are described. Immunodiagnosics methodologies utilized in these kits are modifications of general and specific principles well known in the art. E. Harlow and D. Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, New York, 1988, and E.T. Maggio, Ed., Enzyme-Immunoassay, CRC Press, Florida, 1980 are incorporated by reference herein.

15 Sandwich enzyme immunoassay kit components are as follows: 96-well microtiter plates coated with anti-Wise antibody, diluent buffer, Wise standards, horseradish peroxidase (HRP)-conjugated mouse anti-Wise antibody, ortho-phenylenediamine (OPD) substrate solution, containing H<sub>2</sub>O<sub>2</sub>, and 2N sulfuric acid stop solution.

Competitive enzyme immunoassay kit components are as follows: 96-well microtiter  
20 plates coated with wild type or variant Wise molecules, diluent buffer, Wise wild type and variant standards, horseradish peroxidase (HRP)-conjugated mouse anti-Wise antibody, ortho-phenylenediamine (OPD) substrate solution, containing H<sub>2</sub>O<sub>2</sub>, and 2N sulfuric acid stop solution. Similarly, Sost immunoassay kits may be prepared by substituting anti-Sost antibody for anti-

Wise antibody, and Sost standards for Wise standards as components in the above described Wise kit.

**Example 43.**

In this Example, an immunoprecipitation protocol and subsequent Western Blot protocol  
5 are described for analysis and characterization of various Wise-derived proteins and polypeptide molecules. Similarly, immunoprecipitation and Western blot analysis and characterization may be executed for Sost-derived proteins and polypeptide molecules. Western blot kits based on the methodology described herein may also be produced.

Western blot kits will contain the following components: Wise-derived protein and  
10 polypeptide molecule standards, primary goat antibody against Wise, secondary alkaline phosphatase-conjugated anti-goat antibody, blocking buffer, diluent buffer, and substrate development solution.

The immunoprecipitation protocol involves a technique for separation of Wise-derived polypeptide molecules from whole cell lysates or cell culture supernatants. Wise-derived  
15 polypeptide molecules may be wild type or mutant molecules; and these molecules may be obtained from mammalian cell cultures (*e.g.*, osteoblasts) or from bacterial cells (*e.g.*, *E. coli*) or mammalian cells. After immunoprecipitation binding to anti-Wise antibody and separation of these Wise-derived polypeptide molecules, the Wise molecules can be identified, biochemically characterized, and expression levels quantitated. Sost-derived polypeptide molecules may be  
20 similarly immunoprecipitated.

In initial immunoprecipitation runs, approximately 5-10  $\mu$ g of anti-Wise-derived polypeptide molecule antibody is added to an Eppendorf tube containing the cold precleared lysate containing Wise polypeptides. Alternatively, antibodies recognizing the MYC tag may be

utilized for these immunoprecipitations of Wise polypeptides. Reduced and nonreduced Wise-derived polypeptide molecules are prepared to run alongside prestained molecular weight standards for use on SDS-PAGE gels.

In the R&D System Immunostaining procedure, Western Blot membranes are blocked in  
5 Blocking Buffer, incubated with primary goat anti-Wise polypeptide antibody, incubated with secondary antibody (*e.g.*, alkaline phosphatase conjugated anti-goat IgG antibody), incubated with Substrate Development solution, dried, and blocked in Blocking Buffer. Block unoccupied protein binding sites on membrane by placing membrane in Blocking Buffer on a rocker/shaker. Primary antibody (*e.g.*, goat anti-Wise polypeptide molecule antibody) in Diluent Buffer is  
10 added to the membrane and incubated. After washing, incubate blots with 20 mL of secondary antibody (*e.g.*, TAGO alkaline phosphatase-conjugated rabbit anti-goat IgG antibody) in Diluent Buffer and incubated. Wash membranes, incubate and then add Substrate Development Solution to membrane. Stop substrate development after incubation by pouring off Development Solution and rinsing membrane in deionized water.

15 In summary, this Western blot methodology can be used to identify, biochemically and immunologically characterize, and quantitate Wise and Sost polypeptide molecules derived from wild type and/or mutants in both mammalian and bacterial cell culture systems. In addition, Western blot kits may be produced utilizing Wise-derived and Sost-derived molecule standards, antibodies, and kit components described and utilized in the above-described methodology.

20 **Example 44.**

In this Example, hybridization kits are described for the detection of Wise wild type and Wise variant nucleic acid sequences. Wise wild type and variant nucleic acid sequence molecules are prepared by either PCR methodology [Mullis, U.S. Pat. No. 4,683,195; Mullis,

4,683,202], including real time PCR techniques, or conventional cloning technology as described in Examples 19-20. Probe nucleic acid sequences can be produced in vectors as described previously. As alternatives to PCR methodology, isothermal techniques [Guatelli et al., Proceeding of the National Academy of Science 87: 1874-1878 (1990)], transcription based  
5 methods [Kwoh et al., Proceedings National Academy of Science 86: 1173-1177 (1989)], and QB replicase techniques [Munishkin et al., Nature 33: 473 (1988)] may be used. DNA or RNA primers are prepared containing desired Wise or Sost probe sequences. For example, a nucleic acid probe can be prepared to different portions of Wise nucleic acid sequences. Similarly, probes can be prepared for nucleic acid sequences that encode inactive Wise polypeptide variants  
10 that either do not bind to LRP5 or LRP6 or, alternatively, that, when inserted into mammalian cells, cause phenotypic increases in bone deposition or bone mineral density. [Kemp et al., Proceedings of the National Academy of Science 86: 2423-2427 (1989)].

Wise wild type molecule and Wise variant cDNA synthesis and DIG labeling is as follows: Heat 10-15 µg Wise sample RNA with 1.7 µl random primers (3 ug/ul; Invitrogen Cat.  
15 No. 48190-011) and 15.9 µl H<sub>2</sub>O at 70° C. Snap cool on ice and centrifuge. To each reaction tube, add DIG-dCTP. Add Master mix as follows: First Strand Buffer, DTT, dNTPs (25 mM each dA/G/TTP, 10 mM dCTP), SuperScript II (200 U/ul; Invitrogen Cat. No. 18064-014). Incubate reaction at 25° C, followed by 42° C incubation.

While incubating the above reaction mixture, slides are prepared for hybridization as  
20 follows: Incubate the prehybridization solution in a Coplin jar at 63° C to equilibrate. Place slides in the pre-heated solution and incubate at 63° C. Prepare two staining troughs, one with MilliQ H<sub>2</sub>O and the other with isopropanol. Place slides in slide rack and immerse in first trough to rinse in MilliQ H<sub>2</sub>O with vigorous shaking. Transfer the rack into the second trough and rinse

in isopropanol. Dry slides by centrifugation on a microtiter plate rotor on absorbent cloth. Store slides in slide box prior to hybridization.

Briefly centrifuge the labeling reaction tubes. Add 10  $\mu$ l 1N NaOH and heat at 70° C to hydrolyze the RNA. Neutralize by adding 1 N HCl. Using the MinElute PCR purification kit (Qiagen Cat. No. 28004), combine DIG-labeled cDNA samples in a single Eppendorf tube and add Buffer PB. Apply to MinElute column in collection tube and centrifuge. Purple coloration of the membrane indicates efficient labeling of both cDNA samples. Add 50  $\mu$ l Buffer PE to MinElute column and centrifuge to dry the membrane. Add 10  $\mu$ l MilliQ H<sub>2</sub>O pH 7-8.5 carefully to the center of the membrane and allow to stand for 1 min. Centrifuge to collect cDNA (yield ~ 80%). Place the MinElute column into a fresh tube B. Add MilliQ H<sub>2</sub>O pH 7-8.5 to the center of the membrane and allow to stand for 1 min. Centrifuge at 13,000 rpm for 1 min to collect residual cDNA. Transfer 4.5  $\mu$ l from tube B to tube A (final volume 14.5  $\mu$ l).

For hybridization, the following procedure is used: Mix purified DIG sample with hybridization solution (DIG-labeled cDNA, filtered 20x SSC, filtered 2x SDS). Prepare a slide heating block. Preheat the hybridization chamber. Heat hybridization solution at 99° C for 2 min to denature cDNA. In the meantime, prepare the slide and a 24 x 24 mm coverslip. When ready, immediately centrifuge the hybridization solution briefly, put the slide into the chamber, pipet SSC into each of the two wells of the chamber, and apply the solution onto the slide at the edge of the spotted area avoiding bubble formation by using curved-edge fine forceps to set the coverslip in place. Close the chamber and immerse it in a 63°C waterbath. Incubate chambers overnight.

Transfer slides one at a time from the chamber to the Coplin jar containing Wash A and let the coverslip fall off by gently moving the slide vertically in the solution. Once the coverslip

is removed, transfer the slide quickly to the rack in the trough of Wash A. When all slides are on the rack, wash by vigorous agitation for 5 min at room temperature. Transfer the slides quickly to the rack in the second trough containing Wash B. Wash by vigorous agitation for 3 min at room temperature. Transfer the rack to the third trough containing Wash B and wash by  
5 vigorous agitation for 3 min at room temperature. Dry slides and store in a slide box until scanning.

The ScanArray Express (Perkin Elmer Life Sciences, Boston, MA) can be used to scan the slides. Alternatively, the Image Trak Eip-Fluorescence System (Perkin Elmer Life Sciences, Boston, MA) can be used for 96,384, or 1536 well plates.

10 In summary, hybridization methodology and kits for the detection, identification, and quantification of Wise-associated nucleic acid sequences in cells are set forth herein. Using these methods, Wise wild type and mutant nucleic acid sequences can be identified, characterized, and quantified. In addition, kits may be produced utilizing Wise-derived nucleic acid molecule standards, antibodies, and kit components as described in the above methodology.



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Thus, there has been shown and described novel methods and compositions related to Wise, Sost, and LRP, which influence ocular development, bone deposition, Wnt pathway, and tooth development, which fulfills all the objects and advantages sought therefore. It is apparent to those skilled in the art, however, that many changes, variations, modifications, and other uses and applications for the subject methods and compositions are possible, and also such changes, variations, modifications, and other uses and applications which do not depart from the spirit and scope of the invention are deemed to be covered by the invention, which is limited only by the claims which follow.

What is claimed is:

1. A family of isolated nucleic acid molecules which can influence at least one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development, wherein the family is selected from the group consisting of:

5 (a) isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs 1-8, 10-28, 96, 97, 108 – 111, 126, and 127, and complementary sequences thereof;

(b) degenerate variants of the sequences of step a;

(c) an isolated nucleic acid molecule that expresses a cysteine knot protein; and,

(d) oligonucleotide fragments which are 70% homologous to Exon 2 of SEQ. ID.

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2. The isolated nucleic acid molecule of Claim 1(c), wherein the nucleic acid molecule is selected from the group consisting of Wise and Sost family member nucleic acid sequence molecules.

15 3. The isolated nucleic acid molecule of Claim 1, wherein nucleic acid molecules are homologous to the sequences of Claim 1, and are selected from the group consisting of genes, mRNA, cDNA, gDNA, tRNA, RNAi, SiRNA, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

20 4. The isolated nucleic acid molecules of Claim 1 wherein the molecules comprise genes, mRNA, cDNA, gDNA, tRNA, RNAi, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

5. Antisense RNAs complementary to at least one of the isolated nucleic acid molecules of Claim 1.

6. Mutations of the nucleic acid sequences of Claim 1, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

7. The mutations of Claim 5 wherein the loss of function mutation comprises a stop codon associated with Exon1 of the Wise gene.

5 8. The mutations of Claim 5, wherein the loss of function mutation comprises a stop codon associated with the Sost gene.

9. An antisense oligonucleotide to any mRNA transcribed from at least one nucleic acid molecule of Claim 1.

10. An RNAi complementary to at least one of the nucleic acid sequences of Claim 1.

10 11. RNA nucleic acid molecules transcribed from the nucleic acid sequences of Claim 1.

12. A probe which hybridizes to at least one of the nucleic acid molecules of Claim 1 selected from the group consisting of cDNA and RNA labeled probes.

13. A vector comprising a promoter operably linked to a nucleic acid molecule  
15 according to Claim 1 or 6.

14. The vector of Claim 13, wherein the vector is selected from the group consisting of expression, cloning, and viral vectors.

15. The vector of Claim 13, wherein the vector is selected from the group consisting of expression vectors, fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-  
20 hybrid vectors, sequencing vectors, and cloning vectors.

16. The vector of Claim 13, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

17. The prokaryotic vector of Claim 16, wherein the vector is selected from the group consisting of pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT.

5 18. The eukaryotic vector of Claim 16, wherein the vector is selected from the group consisting of pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis.

10 19. The promoter of Claim 13, wherein the promoter is selected from the group consisting of a viral promoter and a cellular promoter.

20. The vector of Claim 13, wherein the vector comprises a selectable marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, a protein binding site, and an immunoglobulin binding site.

15 21. The vector of Claim 20, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

22. The isolated nucleic acid molecule of Claim 1, wherein nucleic acid molecules homologous to the sequences of Claim 1 are selected from the group consisting of wild type, mutant, antisense, base-substituted, frame shift, deletion, and truncated genes.

20 23. The prokaryotic vector of Claim 17, wherein the vector replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

24. The prokaryotic host cell of Claim 23, wherein the host cell is a bacterium selected from the group consisting of Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas.

25. The Gram-negative bacterium of Claim 23, wherein the bacterium is Escherichia  
5 coli.

26. The eukaryotic vector of Claim 16, wherein the vector replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, mouse, frog, or insect cells.

27. The eukaryotic host cell of Claim 26, wherein the host cell is selected from cells  
10 of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

28. A host cell transfected with a vector according to Claim 13.

29. A morpholino antisense oligo molecule derived from any of the nucleic acid sequences of Claim 1.

15 30. The morpholino of Claim 29, wherein the effective amount of morpholino antisense oligo is within a concentration range between 0.1 nM to 10 mM.

31. A mutant Wise nucleic acid molecule selected from the group consisting of mutants of the following sequences:

(a) isolated nucleic acid molecule selected from the group consisting of SEQ. ID.  
20 NOs. 1-5, 96, 97, 109, 126-128, and complementary sequences thereof;

(b) degenerate variants of the sequences of step a;

(c) an isolated nucleic acid molecule that expresses a cysteine knot protein; and,

(d) oligonucleotide fragments which are 70% homologous to Exon 2 of SEQ. ID.

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32. The mutant nucleic acid sequences of Claim 31, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

5 33. A recombinant Wise plasmid formed from a mutant of Claim 31, a promoter, and a selectable marker.

34. The plasmid of Claim 33 comprising at least one stop codon.

35. A host cell transfected with the plasmid of Claim 33, wherein the host cell comprises stem cells.

10 36. A host cell transfected with the plasmid of Claim 33, wherein the host cell comprises embryonic cells.

37. A chimeric mammal wherein the host cell of Claim 35 or Claim 36 is used to transfect the mammal.

38. The transfected mammal of Claim 37, wherein a mouse is selected.

15 39. The promoter of Claim 33, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

40. The Wise plasmid of Claim 33, wherein the selectable marker comprises at least one marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense  
20 oligonucleotide, a restriction endonuclease, an enzyme cleavage site, an enzyme, a protein binding site, and an immunoglobulin binding site.

41. The Wise plasmid of Claim 33, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

42. The Wise mutant nucleic acid molecule of Claim 31, wherein the sequences are selected from the group consisting of wild type, mutant, antisense, base-substituted, deletion, frameshift, and truncated genes.

43. The vector of Claim 33, wherein the vector is selected from the group consisting  
5 of prokaryotic and eukaryotic vectors.

44. A prokaryotic plasmid of Claim 43, wherein the plasmid replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

45. A prokaryotic host cell transfected with the plasmid of Claim 33, wherein the host  
10 cell is selected from the group consisting of Escherichia, Salmonella, Proteus, Clostridium, Klebsiella, Bacillus, Streptomyces, and Pseudomonas.

46. The Gram-negative bacterium of Claim 43, wherein the bacterium is Escherichia coli.

47. A eukaryotic host cell transfected with the plasmid of Claim 33, wherein the  
15 plasmid replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, frog, or insect cells.

48. The eukaryotic host cell of Claim 47, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

20 49. A mutant Wise nucleic acid molecule which can influence at least one of the following: tooth development, Wnt pathway, bone deposition, and ocular development selected from the group consisting of:



(a) mutants of isolated nucleic acid molecules comprising SEQ. ID. NOs. 1-5, 8, 109, 126 – 128, and complementary sequences thereof;

(b) degenerate variants of the sequences of step a; and,

(c) Wise nucleic acid molecules having a stop codon which prevents translation to a polypeptide.

50. A mutant Sost isolated nucleic acid molecule which can influence at least one of the following: tooth development, Wnt pathway, bone deposition, and ocular development selected from the group consisting of mutant variants of:

(a) Mutants of isolated nucleic acid molecule comprising SEQ. ID. NOs. 6, 7, 9 – 14, 110, and 111, and complementary sequences thereof; and,

(b) degenerate variants of the sequences of step a.

51. The isolated nucleic acid molecule of Claim 50, wherein nucleic acid molecules are homologous to the sequences of Claim 50, and are selected from the group consisting of genes, mRNA, cDNA, gDNA, tRNA, RNAi, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

52. The mutants of Claim 50, wherein the mutants comprise antisense RNAs complementary to the non-mutant isolated nucleic acid molecules.

53. The mutants of Claim 50, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

54. The mutations of Claim 53, wherein the loss of function mutation comprises a stop codon at the start of the Sost gene.

55. An antisense oligonucleotide to any mRNA translated from a nucleic acid molecule of Claim 50.

56. An RNAi complementary to the non-mutant nucleic acid sequences homologous to the sequences of Claim 50.

57. RNA nucleic acid molecules transcribed from the nucleic acid sequences of Claim 50.

58. A probe which hybridizes to at least one of the nucleic acid molecules of Claim 50 selected from the group consisting of cDNA and RNA labeled probes.

59. A vector comprising a promoter operably linked to a nucleic acid molecule according to Claim 50.

60. The vector of Claim 59, wherein the vector is selected from the group consisting of expression, cloning, and viral vectors.

61. The vector of Claim 59, wherein the vector is selected from the group consisting of expression vectors, fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors.

62. The vector of Claim 59, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

63. The prokaryotic vector of Claim 62, wherein the vector is selected from the group consisting of pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280, pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT.

64. The eukaryotic vector of Claim 62 wherein the vector is selected from the group consisting of pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG,

pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis.

65. The promoter of Claim 59, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

5 66. The vector of Claim 59, wherein the vector comprises a selectable marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, a protein binding site, and an immunoglobulin binding site.

10 67. The vector of Claim 66, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

68. The isolated nucleic acid molecule of Claim 50, wherein nucleic acid molecules homologous to the sequences of Claim 50 are selected from the group consisting of wild type, mutant, antisense, base-substituted, frame shift, deletion, and truncated genes.

15 69. The prokaryotic vector of Claim 63, wherein the vector replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

70. The prokaryotic host cell of Claim 69, wherein the host cell is a bacterium selected from the group consisting of *Escherichia*, *Salmonella*, *Proteus*, *Clostridium*, *Klebsiella*, *Bacillus*, *Streptomyces*, and *Pseudomonas*.

20 71. The Gram-negative bacterium of Claim 69, wherein the bacterium is *Escherichia coli*.

72. The eukaryotic vector of Claim 64, wherein the vector replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, mouse, frog, or insect cells.

73. The eukaryotic host cell of Claim 72, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

74. A host cell transfected with a vector according to Claim 59.

75. A morpholino antisense oligo molecule derived from the nucleic acid sequences of Claim 50.

76. The morpholino of Claim 75, wherein the effective amount of morpholino antisense oligo is within a concentration range between 0.1 nM to 10 mM.

77. A mutant LRP nucleic acid molecule which can influence at least one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development, selected from the group consisting of:

- (a) mutants of isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs 29 - 44, 99, 100, 112, 113, and complementary sequences thereof; and,  
(b) degenerate variants of the sequences of step a.

78. The isolated nucleic acid molecule of Claim 77, wherein nucleic acid molecules are homologous to the sequences of Claim 77, and are selected from the group consisting of genes, mRNA, cDNA, gDNA, tRNA, RNAi, oligonucleotides, polynucleotides, and nucleic acid sequence fragments.

79. The mutants of Claim 77, wherein the mutants comprise antisense RNAs complementary to the isolated nucleic acid molecules of Claim 77.

80. The mutations of Claim 77, wherein mutants are selected from the group consisting of point, frame shift, deletion, and loss of function mutations.

5 81. An antisense oligonucleotide to any mRNA translated from a nucleic acid molecule of Claim 77.

82. An RNAi complementary to the nucleic acid sequences homologous to the sequences of Claim 77.

10 83. RNA nucleic acid molecules transcribed from the nucleic acid sequences of Claim 77.

84. A probe which hybridizes to at least one of the nucleic acid molecules of Claim 77 selected from the group consisting of cDNA and RNA labeled probes.

85. A vector comprising a promoter operably linked to a nucleic acid molecule according to Claim 77.

15 86. The vector of Claim 85, wherein the vector is selected from the group consisting of expression, cloning, and viral vectors.

87. The vector of Claim 85, wherein the vector is selected from the group consisting of expression vectors, fusion vectors, gene therapy vectors, two-hybrid vectors, reverse two-hybrid vectors, sequencing vectors, and cloning vectors.

20 88. The vector of Claim 85, wherein the vector is selected from the group consisting of prokaryotic and eukaryotic vectors.

89. The prokaryotic vector of Claim 88, wherein the vector is selected from the group consisting of pET, pET28, pcDNA3.1/V5-His-TOPO, pCS2+, pcDNA II, pSL301, pSE280,

pSE380, pSE420, pTrcHis, pRSET, pGEMEX-1, pGEMEX-2, pTrc99A, pKK223-3, pGEX, pEZZ18, pRIT2T, pMC1871, pKK233-2, pKK38801, and pProEx-HT.

90. The eukaryotic vector of Claim 88, wherein the vector is selected from the group consisting of pFastBac, pFastBac HT, pFastBac DUAL, pSFV, pTet-Splice, pEUK-C1, pPUR, 5 pMAM, pMAMneo, pBI101, pBI121, pDR2, pCMVEBNA, YACneo, pSVK3, pSVL, pMSG, pCH110, pKK232-8, p3'SS, pBlueBacIII, pCDM8, pcDNA1, pZeoSV, pcDNA3, pREP4, pCEP4, and pEBVHis.

91. The promoter of Claim 85, wherein the promotor is selected from the group consisting of a viral promoter and a cellular promoter.

10 92. The vector of Claim 85, wherein the vector comprises a selectable marker selected from the group consisting of an antibiotic resistance gene, a tRNA gene, an auxotrophic gene, a toxic gene, a phenotypic marker, a colorimetric marker, an antisense oligonucleotide, a restriction endonuclease, an enzyme cleavage site, a protein binding site, and an immunoglobulin binding site.

15 93. The vector of Claim 91, wherein the selectable marker is selected from the group consisting of LacZ, neo, Fc, DIG, myc, and FLAG.

94. The isolated nucleic acid molecule of Claim 77, wherein nucleic acid molecules homologous to the sequences of Claim 77 are selected from the group consisting of wild type, mutant, antisense, base-substituted, frame shift, deletion, and truncated genes.

20 95. The prokaryotic vector of Claim 89, wherein the vector replicates in a prokaryotic host cell selected from the group consisting of Gram-negative and Gram-positive bacterium.

96. The prokaryotic host cell of Claim 95, wherein the host cell is a bacterium selected from the group consisting of *Escherichia*, *Salmonella*, *Proteus*, *Clostridium*, *Klebsiella*, *Bacillus*, *Streptomyces*, and *Pseudomonas*.

97. The Gram-negative bacterium of Claim 95, wherein the bacterium is *Escherichia coli*.

98. The eukaryotic vector of Claim 88, wherein the vector replicates in a eukaryotic host cell selected from the group consisting of yeast, plant, fish, mammalian, human, mouse, frog, or insect cells.

99. The eukaryotic host cell of Claim 97, wherein the host cell is selected from cells of the group consisting of ES, COS, HEK 293, CHO, SaOS, osteosarcomas, KS483, MG-63, primary osteoblasts, osteoclasts, and human or mammalian bone marrow stroma.

100. A host cell transfected with a vector according to Claim 85.

101. A morpholino antisense oligo molecule derived from the nucleic acid sequences of Claim 77.

102. The morpholino of Claim 100, wherein the effective amount of morpholino antisense oligo is within a concentration range between 0.1 nM to 10 mM.

103. A mutant nucleic acid molecule, wherein the nucleic acid molecule is selected from the group consisting of mutagenized versions of LRP 1, 2, 5, and 6.

104. A nucleic acid sequence comprising a stop codon and a sequence selected from the group consisting of SEQ. ID. NOs. 1 – 44, 96 – 103, 108, 110 – 113, and 126 - 128.

105. A mutant of Wise SEQ. ID. NO. 126.

106. A mutant of mouse Wise nucleic acid SEQ. ID. NO. 1.

107. A mutant chick Wise protein SEQ. ID. NO. 4.
108. A mutant of Wise SEQ. ID. NO. 128.
109. A mutant of Wise SEQ. ID. NO. 2.
110. A mutant of Wise SEQ. ID. NO. 96.
- 5 111. A mutant of Wise SEQ. ID. NO. 97.
112. A mutant of Sost SEQ. ID. NO. 6.
113. A mutant of Sost SEQ. ID. NO. 8.
114. A mutant of Sost SEQ. ID. NO. 10.
115. A mutant of LRP SEQ. ID. NO. 38.
- 10 116. A mutant of LRP SEQ. ID. NO. 39.



117. A family of amino acid sequences which can influence at least one of the following: tooth development, Wnt pathway activation, bone deposition, or ocular development, selected from the group consisting of:

5 (a) an isolated amino acid sequence comprising SEQ ID NOs 45-48, 50-66, 104 – 107, 114 - 125;

(b) Wise amino acid sequences;

(c) Sost amino acid sequences;

(d) LRP amino acid sequences;

10 (e) an isolated amino acid sequence that is at least 70% homologous, to any of the proteins of (a); and,

(f) an isolated protein that has a cysteine knot formed from eight cysteine residues.

118. An antibody which binds to at least one of the amino acid sequences of Claim

15 117.

119. The antibodies of Claim 118, wherein the antibodies are selected from the group consisting of monoclonal antibody, polyclonal antibody, recombinant antibody, and antibody fragment.

120. A hybridoma cell that expresses at least one the antibodies of Claim 118.

20 121. An antibody that binds to a Wise polypeptide.

122. An antibody that binds to a Sost polypeptide.

123. An antibody that selectively binds to an epitope in the receptor-binding domain of the Wise protein.

124. The antibody of Claim 123, wherein an epitope on the Wise protein comprises a cysteine knot sequence that binds LRP, wherein the antibody prevents binding of the Wise protein to the LRP.

125. An Fab fragment derived from an antibody of Claim 118.

5 126. An anti-peptide antibody that prevents binding by Wise amino acid sequences to an LRP polypeptide selected from SEQ. ID. NOs. 67 - 95.

127. A Fab fragment that binds to any one of the polypeptides of Claim 117.

128. Fab fragments which bind to Exon 2 of Wise.

10 129. An anti-peptide antibody that prevents binding by Sost amino acid sequences to an LRP polypeptide selected from SEQ. ID. NOs. 67 - 95

130. A family of amino acid sequences selected from the group consisting of:

(a) an isolated amino acid sequence comprising SEQ ID NOS 45-53, 104 – 107,  
114 - 125;

(b) Wise amino acid sequences; and,

15 (c) SOST amino acid sequences.

131. An antibody that binds to at least one of the amino acid sequences of Claim 130.

132. A Fab fragment from an antibody of Claim 131.

133. An isolated amino acid sequence selected from the group consisting of:

20 (a) an isolated amino acid sequence comprising SEQ ID NOS 45, 52, 104, 105, 106, 114 - 125;

(b) a Wise amino acid sequence encoded by any of the nucleic acid molecules of Claim 1; and,

(c) an isolated protein that has a cysteine knot formed from eight cysteine residues.

134. An antibody that binds to at least one of the amino acid sequences of Claim 133.

135. A Fab fragment from an antibody of Claim 134.

5 136. A family of amino acid sequences selected from the group consisting of:

(a) an isolated amino acid sequence comprising SEQ. ID. NOs. 46 – 51, 53, 109;  
and,

(b) a SOST amino acid sequence.

137. An antibody that binds to at least one of the amino acid sequences of Claim 136.

10 138. A Fab fragment from the antibody of Claim 137.

139. An anti-peptide antibody that prevents binding by a Sost amino acid sequences to  
an LRP polypeptide selected from SEQ. ID. NOs. 67 - 95.

140. An isolated amino acid sequence selected from the group consisting of:

(a) isolated amino acid sequences comprising SEQ. ID. NOs. 67 - 95;

15 (b) LRP polypeptides selected from the group consisting of LRP 1, 2, 5, and 6.

141. An antibody that binds to at least one of the amino acid sequences of Claim 140.

142. A Fab fragment from an antibody of Claim 141.

143. An isolated mutant amino acid sequence selected from the group consisting of:

(a) isolated mutagenized versions of amino acid sequences selected from SEQ.  
20 ID. NOs. 45 – 48, 50 – 66, 104 – 107, 114 - 125;

(b) mutagenized Wise amino acid sequences; and,

(c) mutagenized Sost amino acid sequences.

144. An antibody that binds to at least one of the amino acid sequences of Claim 143.

145. A Fab fragment from an antibody of Claim 144.
146. An isolated antibody derived from the group of polypeptides consisting of:
- (a) an isolated amino acid sequence comprising SEQ. ID. NOs. 45 – 95, 104 – 107, and 114 - 125;
  - 5 (b) anti-Wise antibodies;
  - (c) anti-Sost antibodies; and,
  - (d) LRP antibodies.
147. A host cell transfected invitro with an antibody of Claim 146.
148. A host cell transfected invivo with an antibody of Claim 146.
- 10 149. An Fab derived from one of the antibodies of Claim 146.
150. An Fab which prevents binding of Sost to LRP where in the Fab is derived from a Sost antibody.
151. An Fab which prevents binding of Wise to LRP when the Fab is derived from a Wise antibody.
- 15 152. A protein molecule comprising:
- (a) a Wise polypeptide; and,
  - (b) an LRP polypeptide.
153. The protein of Claim 152, wherein the LRP polypeptide is selected from the group consisting of LRP 1, 2, 5, and 6 polypeptides.
- 20 154. A protein molecule comprising:
- (a) a Sost polypeptide; and,
  - (b) an LRP polypeptide.
155. A method for increasing bone deposition, comprising:

(a) isolating a Wise nucleic acid sequence;

(b) attaching a stop codon at the beginning of the Wise nucleic acid sequence to form a Wise cassette;

(c) forming a Wise plasmid by inserting the Wise cassette into the plasmid;

5 (d) transfecting a host cell with the Wise plasmid, whereby homologous recombination occurs with a wild type Wise gene; and,

(e) activating the stop codon to cause a loss of function mutation.

156. The method of Claim 155, wherein the host cell is selected from the group consisting of an insect, an amphibian, and a non-human mammal.

10 157. The method of Claim 150, wherein the host cell is derived from a human.

158. The method of Claim 155, wherein expression is controlled by delivery of a Wise nucleic acid molecule into a host cell by a method selected from the group consisting of transfection, microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

15 159. The method of Claim 155, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

160. The method of Claim 155 comprising transfecting a host organism to form a chimeric host.

161. The method of Claim 160, wherein the chimeric host is a mouse.

20 162. The method of Claim 160, wherein the host cells are transfected *in vitro*.

163. A method for increasing bone deposition, comprising:

(a) isolating a Sost nucleic acid sequence;

(b) attaching a stop code at the beginning of the Sost nucleic acid sequence to form a Sost cassette;

(c) forming a Sost plasmid by inserting the Sost cassette into the plasmid;

(d) transfecting a host cell with the Sost plasmid, whereby homologous recombination occurs with a wild type Sost gene; and,

(e) activating the stop code to cause a loss of function mutation.

164. The method of Claim 163, wherein the host cell is selected from the group consisting of an insect, an amphibian, and a non-human mammal.

165. The method of Claim 163, wherein the host cell is derived from a human.

166. The method of Claim 163, wherein expression is controlled by delivery of a nucleic acid molecule into a host cell by a method selected from the group consisting of microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

167. The method of Claim 163, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

168. The method of Claim 163 comprising transfecting a host organism to form a chimeric host.

169. The method of Claim 168, wherein the chimeric host is a mouse.

170. The method of Claim 163, wherein the host cells are transfected *in vitro*.

171. A method for increasing bone deposition, comprising:

(a) isolating a LRP nucleic acid sequence;

(b) attaching a stop code at the beginning of the LRP nucleic acid sequence to form an LRP cassette;

(c) forming an LRP plasmid by inserting the LRP cassette into the plasmid;

(d) transfecting a host cell with the LRP plasmid, whereby homologous recombination occurs with a wild type LRP gene; and,

(e) activating the stop code to cause a loss of function mutation.

172. The method of Claim 171, wherein the LRP is selected from the group consisting  
5 of LRP 1, 2, 5, and 6.

173. The method of Claim 171, wherein expression is controlled by delivery of an LRP nucleic acid molecule into a host cell by a method selected from the group consisting of transfection, microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

10 174. The method of Claim 171, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

175. The method of Claim 171 comprising transfecting a host organism to form a chimeric host.

176. The method of Claim 175, wherein the chimeric host is a mouse.

15 177. The method of Claim 171, wherein the host cells are transfected *in vitro*.

178. A method for affecting the Wnt pathway comprising:

(a) isolating a Wise nucleic acid sequence;

(b) attaching a stop code at the beginning of the Wise nucleic acid sequence to form a Wise cassette;

20 (c) forming a Wise plasmid by inserting the Wise cassette into the plasmid;

(d) transfecting a host cell with the Wise plasmid, whereby homologous recombination occurs with a wild type Wise gene; and,

(e) activating the stop code to cause a loss of function mutation.

179. A method for affecting the Wnt pathway comprising:

- (a) isolating a Sost nucleic acid sequence;
- (b) attaching a stop codon at the beginning of the Sost nucleic acid sequence to form a Sost cassette;
- (c) forming a Sost plasmid by inserting the Sost cassette into the plasmid;
- (d) transfecting a host cell with the Sost plasmid, whereby homologous recombination occurs with a wild type Sost gene; and,
- (e) activating the stop code to cause a loss of function mutation.

180. A method for affecting the Wnt pathway comprising:

- (a) isolating an LRP nucleic acid sequence;
- (b) attaching a stop codon at the beginning of the LRP nucleic acid sequence to form an LRP cassette;
- (c) forming an LRP plasmid by inserting the LRP cassette into the plasmid;
- (d) transfecting a host cell with the LRP plasmid, whereby homologous recombination occurs with a wild type LRP gene; and,
- (e) activating the stop code to cause a loss of function mutation.

181. A method for affecting tooth development comprising:

- (a) isolating a Wise nucleic acid sequence;
- (b) attaching a stop code at the beginning of the Wise nucleic acid sequence to form a Wise cassette;
- (c) forming a Wise plasmid by inserting the Wise cassette into the plasmid;
- (d) transfecting a host cell with the Wise plasmid, whereby homologous recombination occurs with a wild type Wise gene; and,



(e) activating the stop code to cause a loss of function mutation.

182. A method for affecting tooth development comprising:

(a) isolating a Sost nucleic acid sequence;

(b) attaching a stop code at the beginning of the Sost nucleic acid sequence to  
5 form a Sost cassette;

(c) forming a Sost plasmid by inserting the Sost cassette into the plasmid;

(d) transfecting a host cell with the Sost plasmid, whereby homologous  
recombination occurs with a wild type Sost gene; and,

(e) activating the stop code to cause a loss of function mutation.

10 183. A method for affecting tooth development comprising:

(a) isolating an LRP nucleic acid sequence;

(b) attaching a stop code at the beginning of the LRP nucleic acid sequence to  
form an LRP cassette;

(c) forming an LRP plasmid by inserting the LRP cassette into the plasmid;

15 (d) transfecting a host cell with the LRP plasmid, whereby homologous  
recombination occurs with a wild type LRP gene; and,

(e) activating the stop code to cause a loss of function mutation.

184. The method of Claim 183, wherein the plasmid includes a promoter.

185. The method of Claim 183, wherein the transfected host cell is delivered to a host  
20 organism to form a knockout host.

186. A method for predicting a defect in bone deposition, comprising:

(a) isolating a Wise gene;

(b) forming a labeled Wise gene probe; and,

(c) contacting the labeled gene probe with DNA from a homologue, whereby attachment of the labeled probe indicates a significant probability of normal bone development with normal activation of the Wnt pathway.

187. A method for causing increased bone deposition comprising:

(a) isolating a nucleic acid sequence selected from the group consisting of Wise, Sost, and LRP; and,

(b) forming an antisense RNA from the nucleic acid sequence;

(c) forming an antisense RNA vector; and,

(d) transfecting a host cell with the antisense RNA vector.

188. The method of Claim 187, wherein the host cell is selected from the group of animals consisting of insect, amphibian, and non-human mammal.

189. The method of Claim 187, wherein the host cell is from Homo sapiens.

190. The method of Claim 187, wherein expression is controlled by injection of an encoding nucleic acid molecule into an embryo.

191. The method of Claim 187, wherein the vector is inserted into a prenatal subject.

192. A method for increasing bone deposition comprising:

(a) isolating a Wise nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Wise nucleic acid sequence to produce Wise polypeptides;

(c) harvesting the Wise polypeptides;

(d) immunizing a host organism with the Wise polypeptides;

(e) isolating antibodies to the Wise polypeptides from the host;

(f) combining the antibodies with a carrier; and,

(g) transfecting a host cell *in vitro*.

193. The method of Claim 192, wherein a host organism is transfected with the carrier containing the antibodies.

194. The method of Claim 192, wherein the host cell is transfected *in vivo*.

5 195. The method of Claim 192, wherein expression is controlled by delivery of a Wise nucleic acid molecule into a host cell by a method selected from the group consisting of transfection, microinjection, micro-vessel encapsulation, liposome encapsulation, and electroporation.

10 196. The method of Claim 192, wherein the host cell is selected from the group consisting of osteoblasts and osteoclasts.

197. The method of Claim 192, wherein the antibodies are Fab fragments.

198. A method for increasing bone deposition comprising:

(a) isolating a Sost nucleic acid sequence;

15 (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Sost nucleic acid sequence to produce Sost polypeptides;

(c) immunizing a host organism with the Sost polypeptides;

(d) isolating antibodies to the Sost polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

20 199. A method for increasing bone deposition comprising:

(a) isolating an LRP nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the LRP nucleic acid sequence to produce LRP polypeptides;

- (c) immunizing a host organism with the LRP polypeptides;
- (d) isolating antibodies to the LRP polypeptides from the host;
- (e) combining the antibodies with a carrier; and,
- (f) transfecting a host cell *in vitro*.

5        200. A method for affecting the Wnt pathway comprising:

- (a) isolating a Wise nucleic acid sequence;
- (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Wise nucleic acid sequence to produce Wise polypeptides;
- (c) immunizing a host organism with the Wise polypeptides;
- 10        (d) isolating antibodies to the Wise polypeptides from the host;
- (e) combining the antibodies with a carrier; and,
- (f) transfecting a host cell *in vitro*.

201. A method for affecting the Wnt pathway comprising:

- (a) isolating a Sost nucleic acid sequence;
- 15        (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Sost nucleic acid sequence to produce Sost polypeptides;
- (c) immunizing a host organism with the Sost polypeptides;
- (d) isolating antibodies to the Sost polypeptides from the host;
- (e) combining the antibodies with a carrier; and,
- 20        (f) transfecting a host cell *in vitro*.

202. A method for affecting the Wnt pathway comprising:

- (a) isolating an LRP nucleic acid sequence;

(b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the LRP nucleic acid sequence to produce LRP polypeptides;

(c) immunizing a host organism with the LRP polypeptides;

(d) isolating Fab antibodies to the LRP polypeptides from the host;

5 (e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

203. A method for affecting tooth development comprising:

(a) isolating a nucleic acid sequence selected from the group consisting of Wise, Sost, and LRP;

10 (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the nucleic acid sequence to produce polypeptides;

(c) immunizing a host organism with the polypeptides;

(d) isolating antibodies to the polypeptides from the host;

(e) combining the antibodies with a carrier; and,

15 (f) transfecting a host cell *in vivo*.

204. A method for affecting ocular development comprising:

(a) isolating a nucleic acid sequence selected from the group consisting of Wise, Sost, and LRP;

20 (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the nucleic acid sequence to produce polypeptides;

(c) immunizing a host organism with the polypeptides;

(d) isolating antibodies to the polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vivo*.

205. A method for preventing Sost from binding to an LRP selected from the group consisting of LRP5 and LRP6 comprising:

(a) isolating a Sost nucleic acid sequence;

5 (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Sost nucleic acid sequence to produce Sost polypeptides;

(c) immunizing a host organism with the Sost polypeptides;

(d) isolating antibodies to the LRP polypeptides from the host;

(e) combining the antibodies with a carrier; and,

10 (f) transfecting a host cell *in vivo*.

206. A method for preventing Wise from binding to an LRP selected from the group consisting of LRP5 and LRP6 comprising:

(a) isolating a Wise nucleic acid sequence;

15 (b) forming a plasmid vector and transfecting a host cell whereby the host cell expresses the Wise nucleic acid sequence to produce Wise polypeptides;

(c) immunizing a host organism with the Wise polypeptides;

(d) isolating antibodies to the Wise polypeptides from the host;

(e) combining the antibodies with a carrier; and,

(f) transfecting a host cell *in vitro*.

20 207. A method for affecting either bone deposition, ocular development, Wnt pathway, or tooth development, comprising transfecting a host cell with an antibody derived from the group consisting of antibodies to LRP, Wise, and Sost, wherein the antibody prevents wild-type polypeptides from binding with their targets.

208. A kit for detecting a Wise polypeptide, wherein the kit comprises:

- (a) a container; and,
- (b) a Wise antibody with a marker.

209. A kit for detecting a Wise nucleic acid molecule, wherein the kit comprises:

- (a) a container; and,
- (b) a Wise probe.

210. The method of Claim 207, wherein the protein molecule is isolated from a host organism in the group selected from Humans, xenopus, frogs, and *Drosophila*.

211. A method for blocking Wise/SOST expression using a morpholino.

212. The kit of Claim 208, wherein the markers comprise en2, Krox20, Hoxb9, myosin, RT-PCR, Ef1-Δ, NCAM, otx2, myosin light chain, and muscle actin.

213. The method of Claim 208, wherein the markers are selected from the group consisting of posterior, midbrain, hindbrain, spinal cord, mesoderm, muscle, and neural markers.

214. A Wise nucleic acid sequence comprising Wise, hemagglutinin, myc, stop codon, and FLAG sequences.

215. A method for activating canonical Wnt signaling comprising:

(a) injecting a Wise protein into an embryo, wherein the Wise protein binds to a Frizzled receptor thereby inhibiting the binding of the Wnt protein to the Frizzled receptor; and,

(b) activating canonical Wnt signaling.

216. A family of nucleic acid sequences selected from the group consisting of Caronte, Wise, Sost Dan, Cereberus, Gremlin, CTGF, Soggy, DKK1, DKK2, DKK3, DKK4, NOV, mucin, slit, OH, WISP, and CCN.

217. A method for producing a Wise mutant mouse comprising:

(a) introducing a mutant Wise gene into a mouse embryonic stem cell;

(b) introducing the embryonic stem cell into a mouse blastocyst to create a transgenic embryo; and,

5 (c) allowing the embryo to develop into the Wise mouse.

218. The method of Claim 217, wherein the introduction of a gene into the stem cell is selected from the group of methods consisting of transfection, micro-injection, biolistic particle delivery, lipofection, and electroporation.

219. The method of Claim 217, wherein the Wise mouse exhibits developmental  
10 abnormalities selected from the group consisting of bone deposition, dental, neurological, and ocular abnormalities.

220. The mutated Wise gene of Claim 217, wherein the gene is selected from the group consisting of antisense, base-substituted, and truncated gene sequences.

221. An isolated mouse cell comprising a mutated Wise gene, wherein the endogenous  
15 wild type Wise gene has been replaced with the mutated Wise gene.

222. The mutated Wise gene of Claim 221, wherein the gene is selected from the group consisting of antisense, base-substituted, and truncated genes.

223. A Wise pET vector comprising a mutated Wise gene sequence, neo, and LacZ.

224. The mutated Wise sequence of Claim 223, wherein the gene sequence is selected  
20 from the group consisting of antisense, base-substituted, and truncated sequences.

225. A Sost pET vector comprising a mutated Sost sequence, neo, and LacZ.

226. The mutated Sost sequence of Claim 225, wherein the gene sequence is selected from the group consisting of antisense, base-substituted, and truncated sequences.



227. A mutant Wise mouse comprising the mutant Wise nucleic acid sequence of Claim 31.

228. The Wise mouse of Claim 227, wherein the mutant Wise gene is selected from the group consisting of homozygous and heterozygous genes.

5 229. A Sost mouse comprising the mutant Sost gene sequence of Claim 49.

230. The Sost mouse of Claim 229, wherein the mutant Sost gene is selected from the group consisting of homozygous and heterozygous genes.

231. A mutant Wise mouse made by the steps comprising:

(a) introducing a mutant Wise gene into a mouse embryonic stem cell;

10 (b) introducing the embryonic stem cell into a mouse blastocyst to create a transgenic embryo; and,

(c) allowing the embryo to develop into the mutant Wise mouse.

232. A family of nucleic acid sequences which can influence at least one of the following: bone deposition, Wnt pathway, tooth development, and ocular development, selected  
15 from the group consisting of SEQ. ID. NOs. 1 - 44.

233. An isolated nucleic acid sequence which regulates bone deposition, ocular development, Wnt pathway, and tooth development, and binds to LRP.

234. The isolated nucleic acid sequence of Claim 233, wherein the sequence is selected from the group consisting of Wise and Sost nucleic acid sequences.

20 235. A method for producing a transgenic mutant Wise mouse, comprising:

(a) microinjecting a Wise cassette containing a mutant Wise nucleic acid sequence into a blastomere;

(b) injecting the blastomere into a host mouse embryo; and,

(c) growing the embryo to maturation.

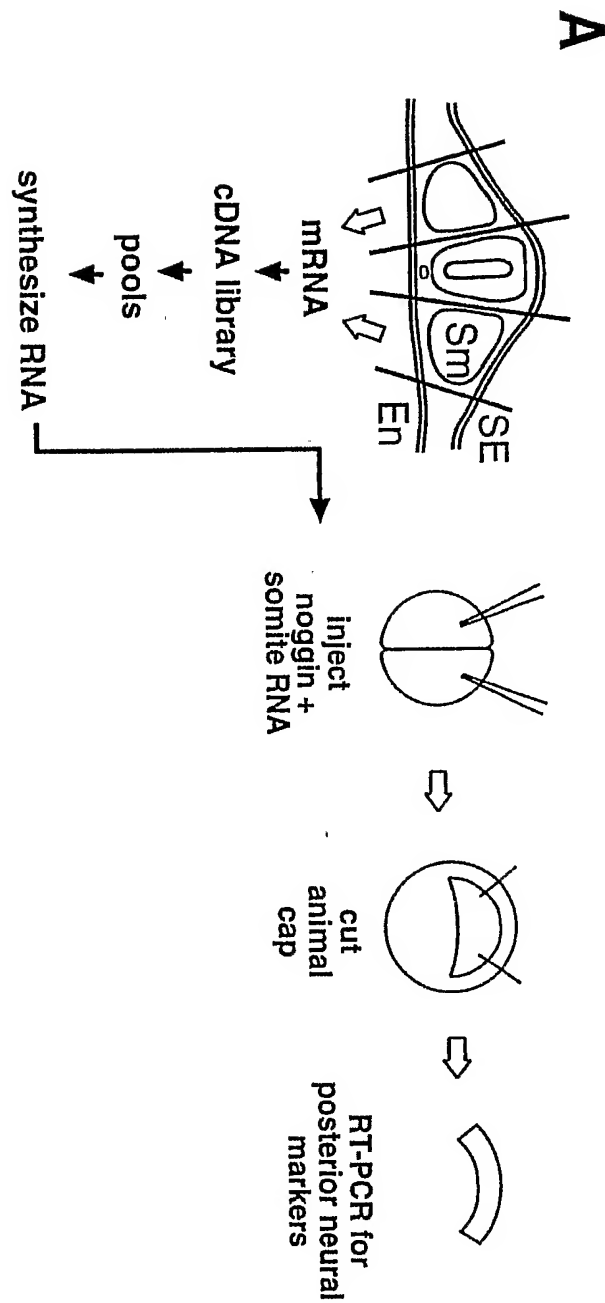


Fig. 1A

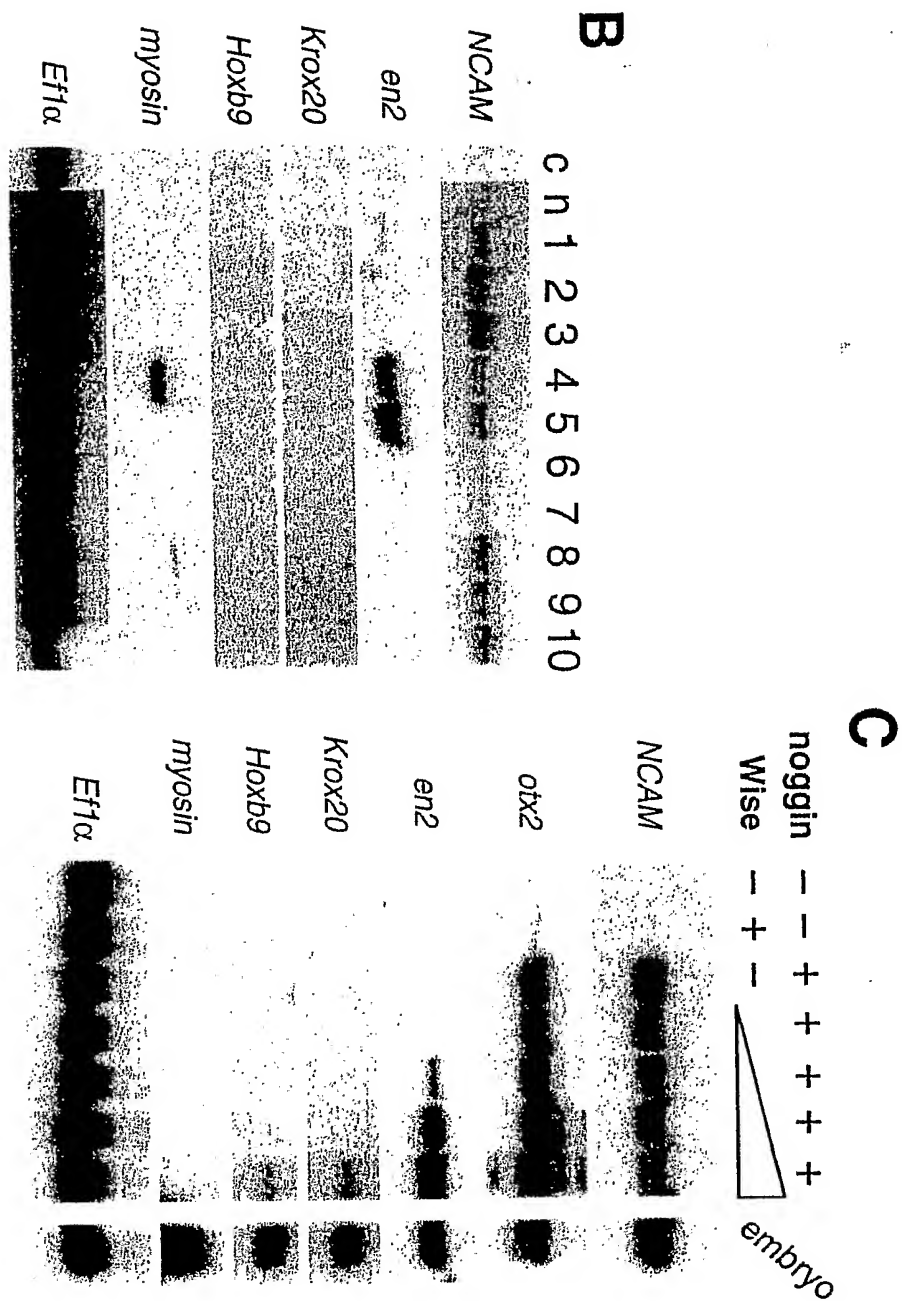


Fig. 1B and C

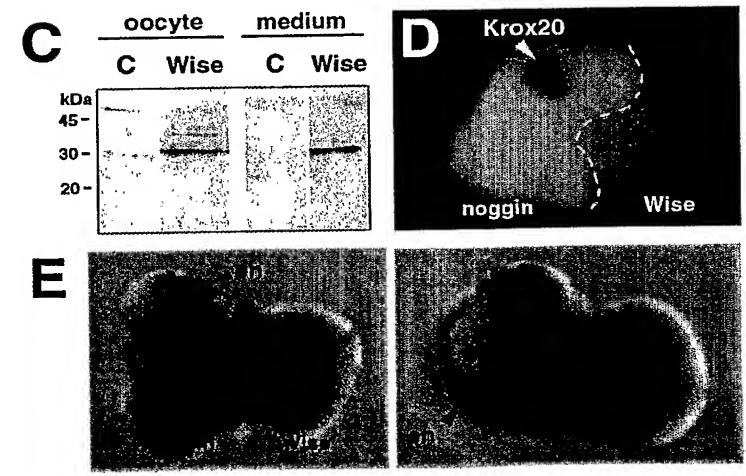
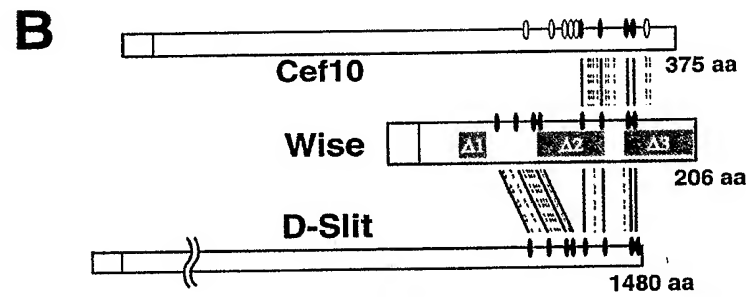
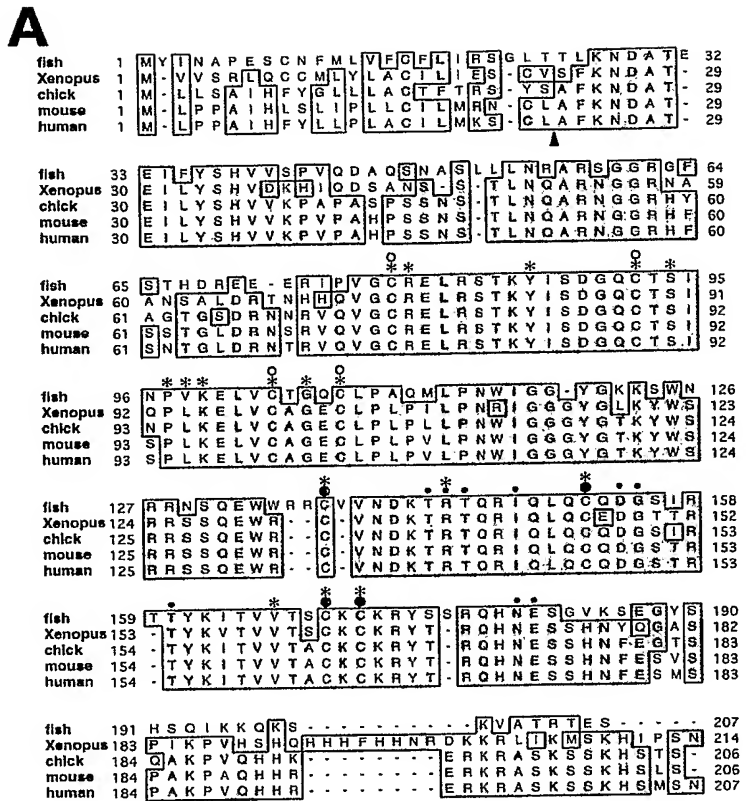


Fig 2

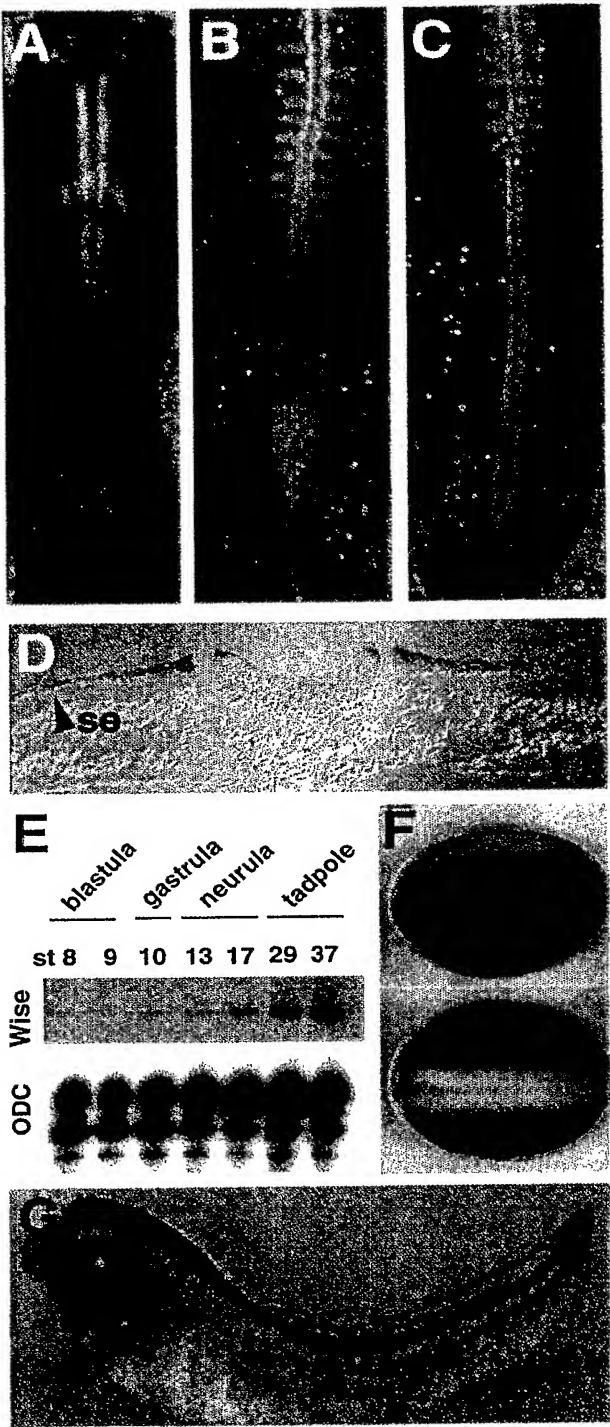


Fig 3

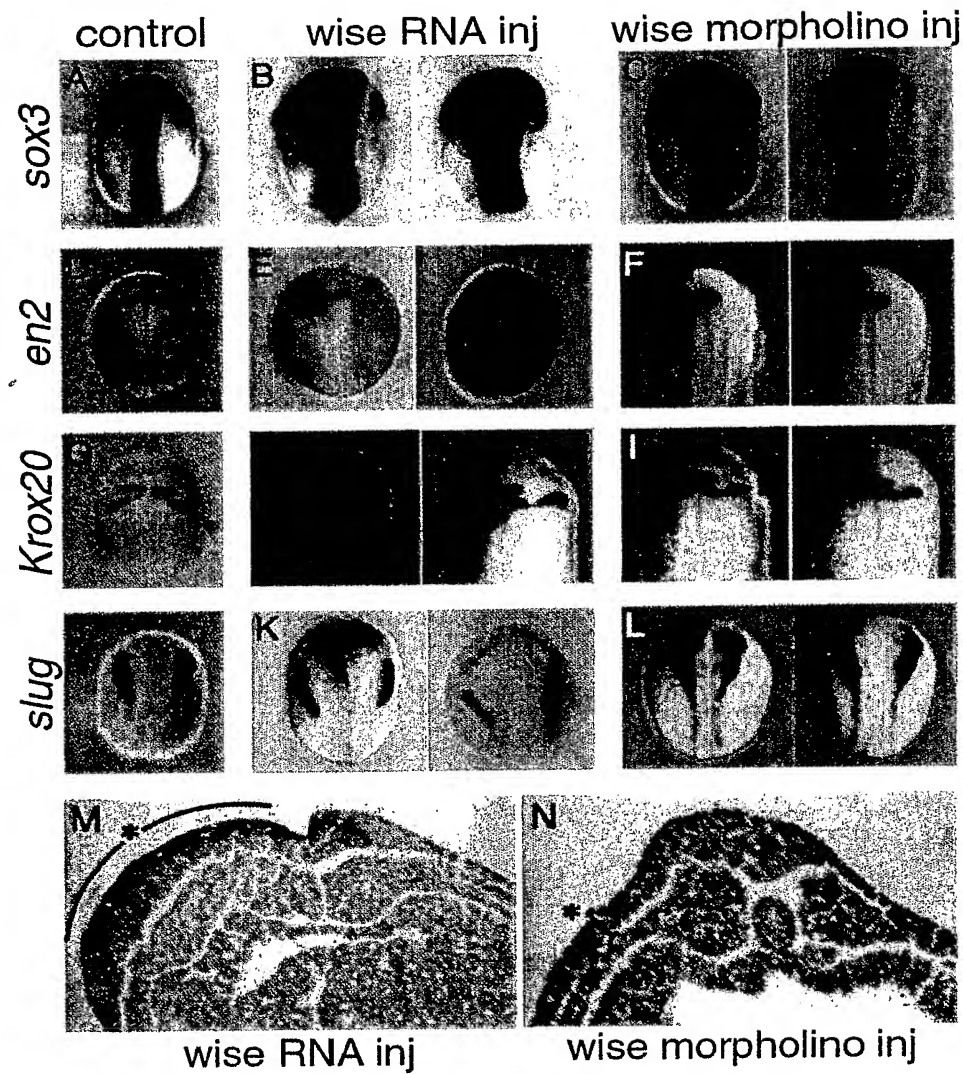


Fig 4

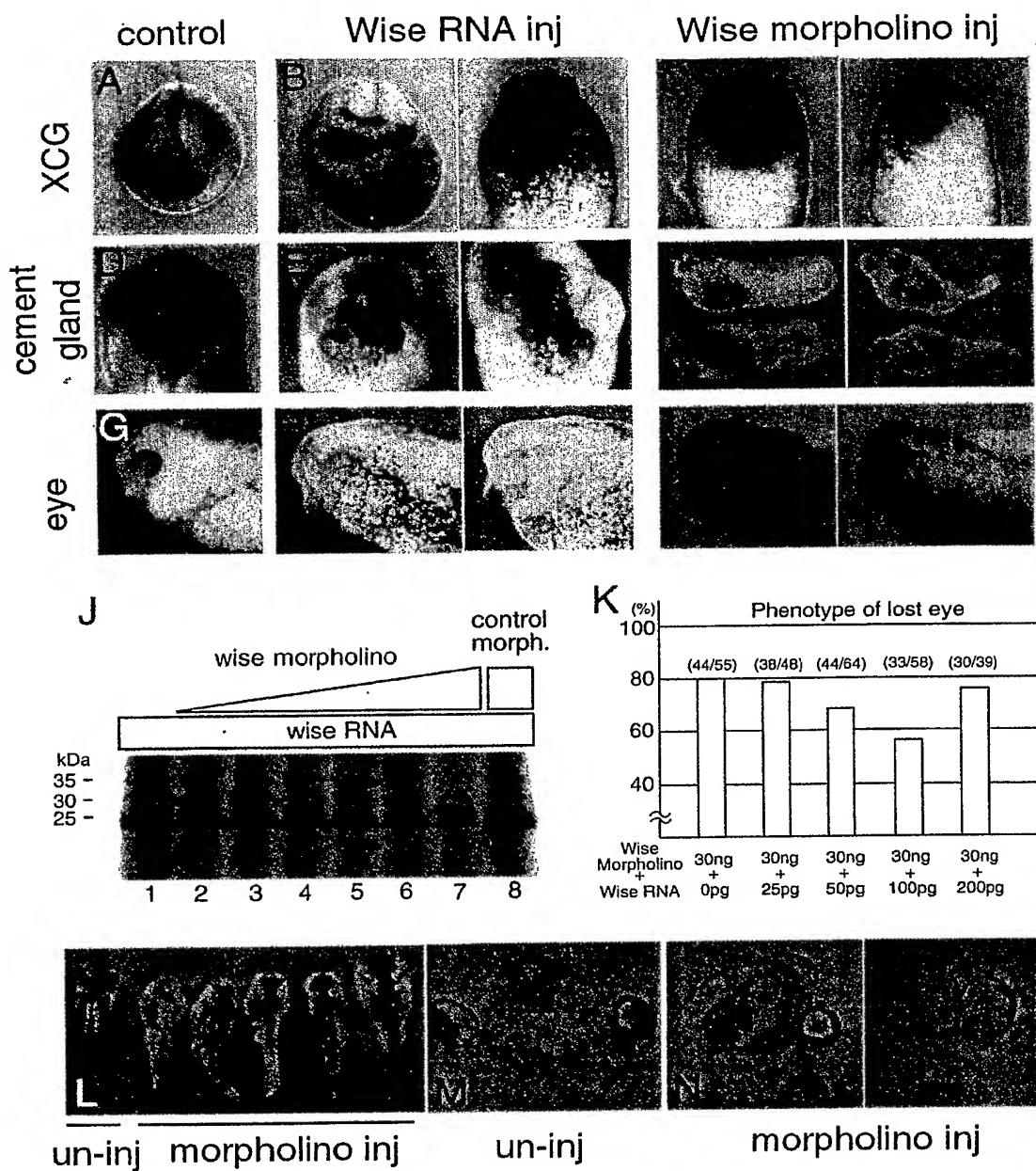
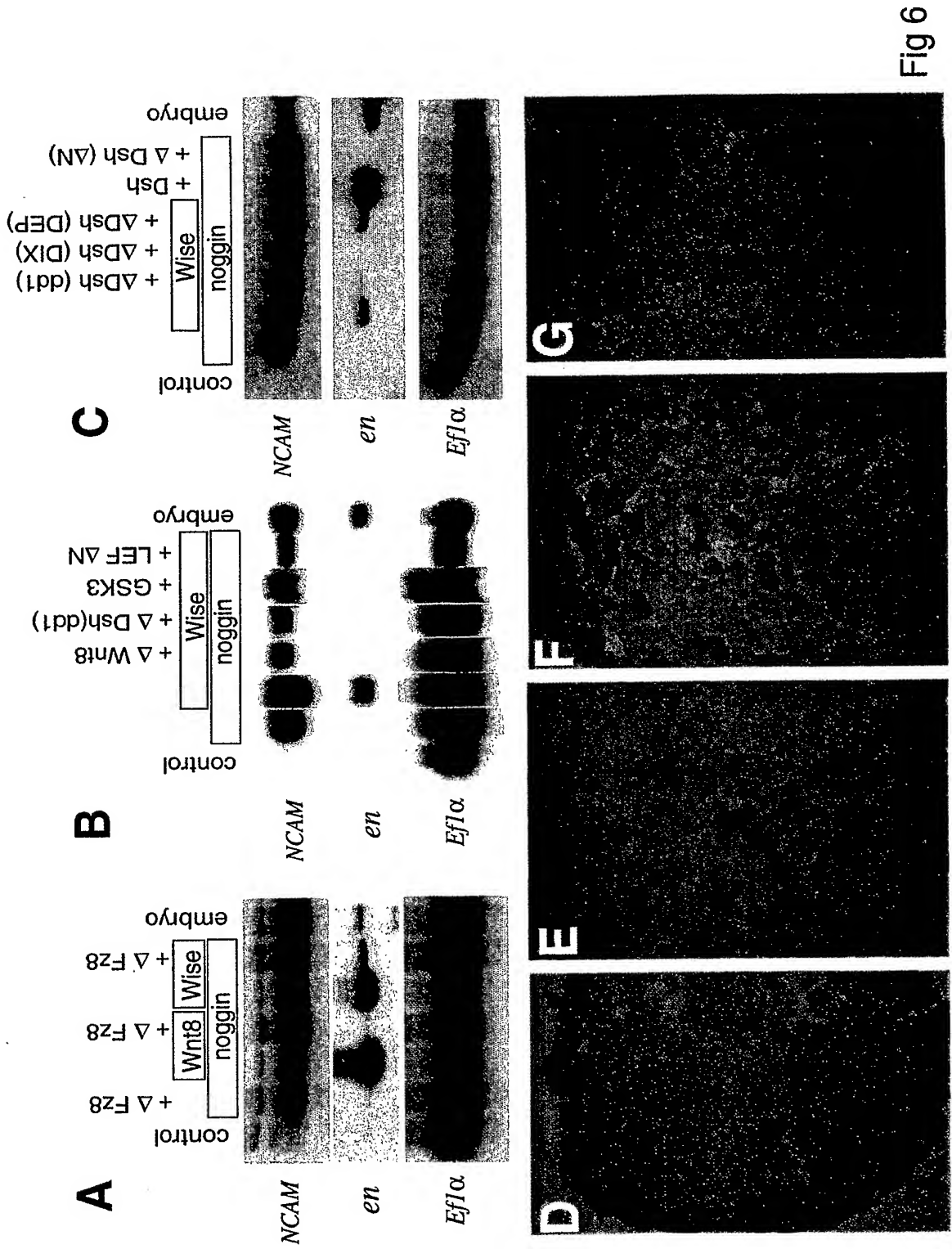


Fig 5





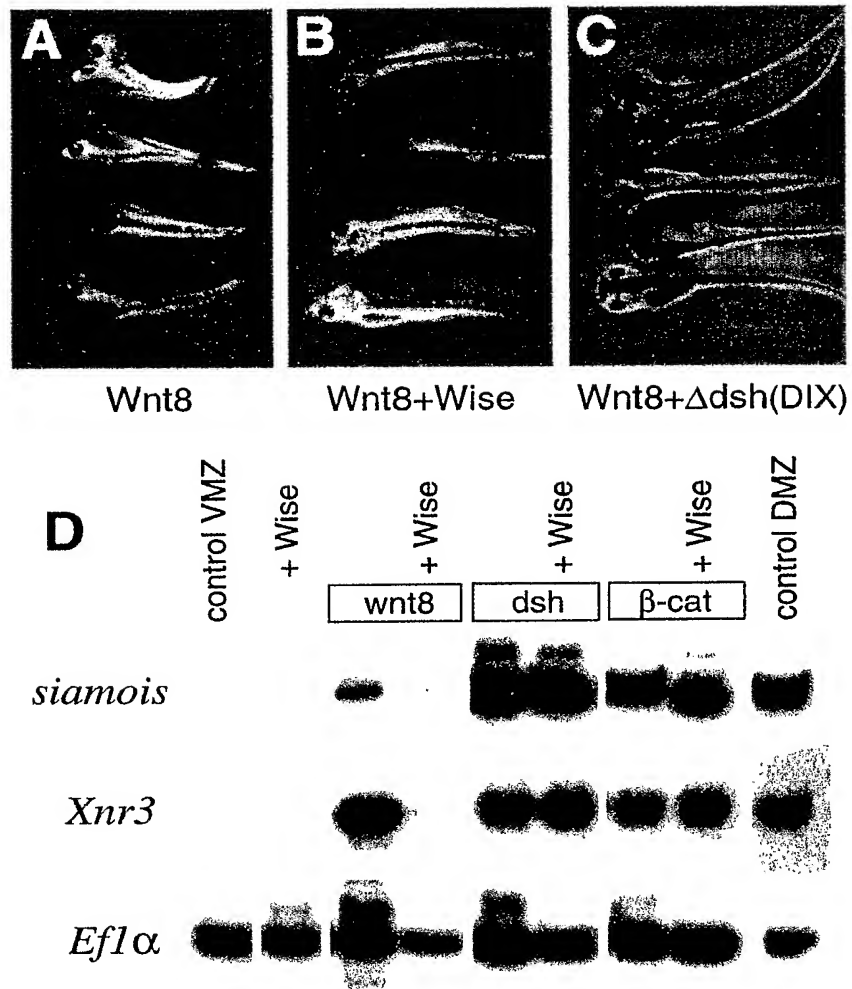


Fig. 7 A-D

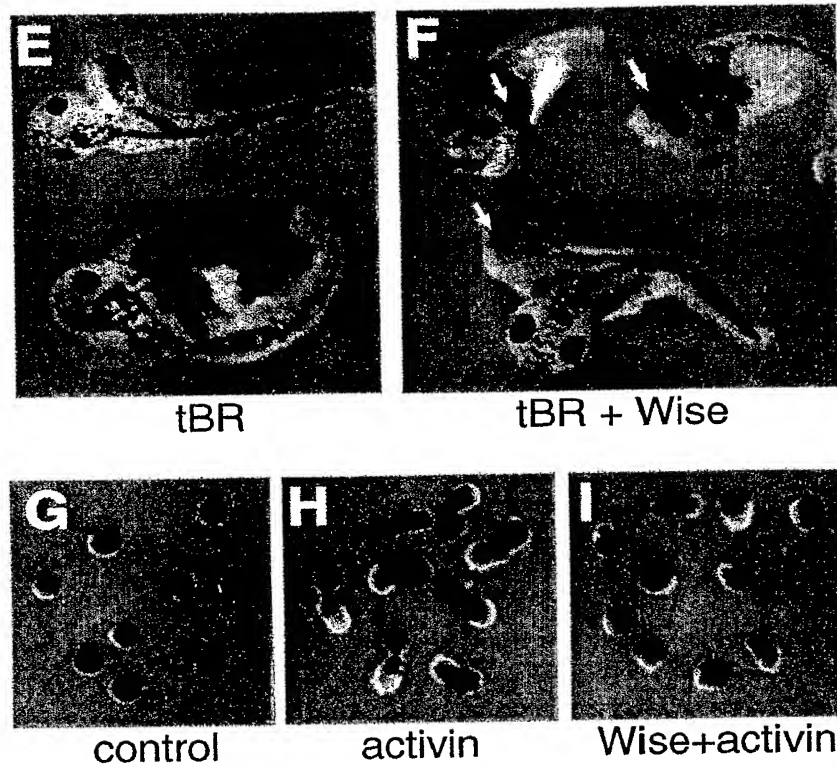


Fig. 7E - I

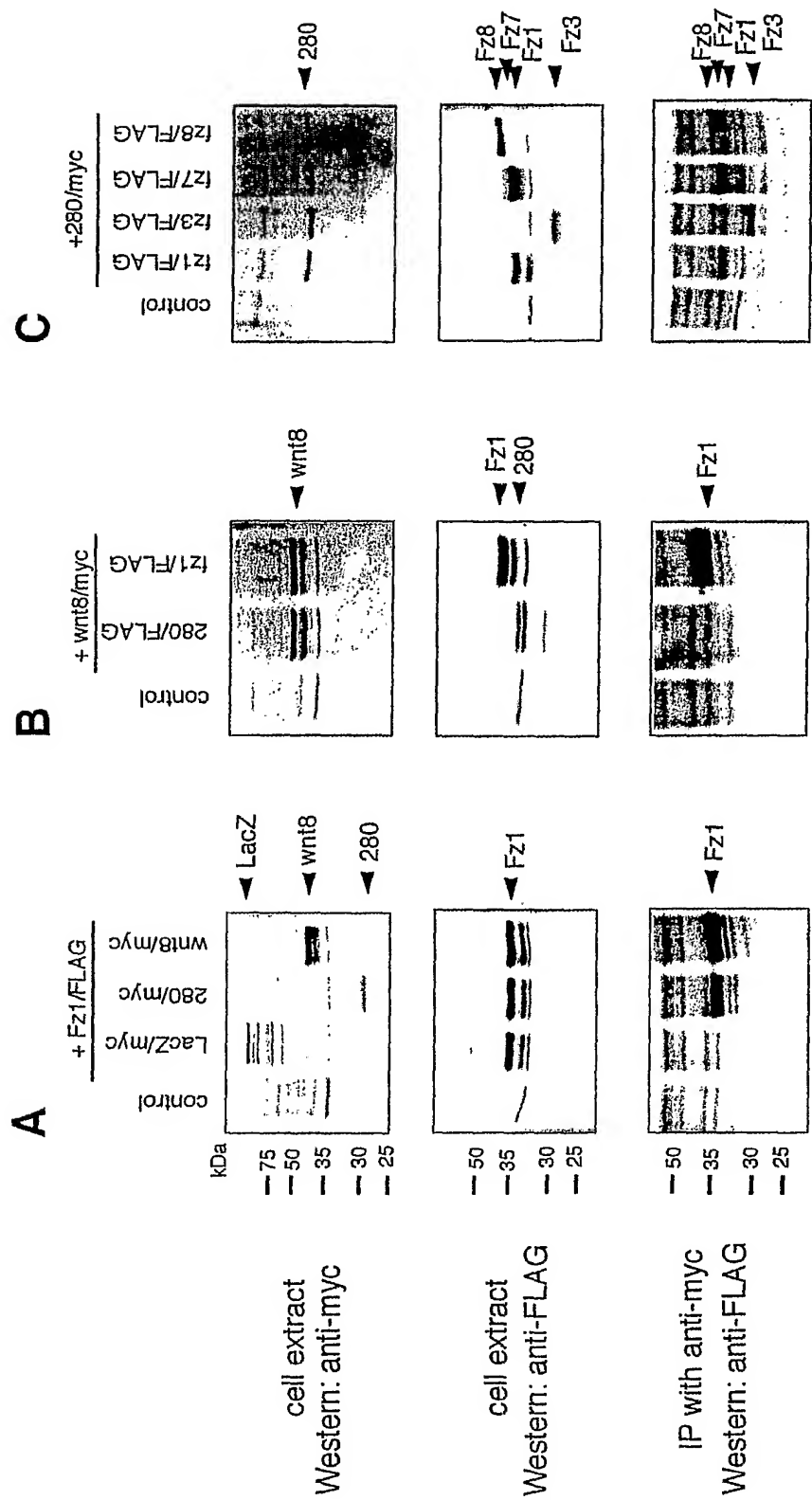


Fig. 8

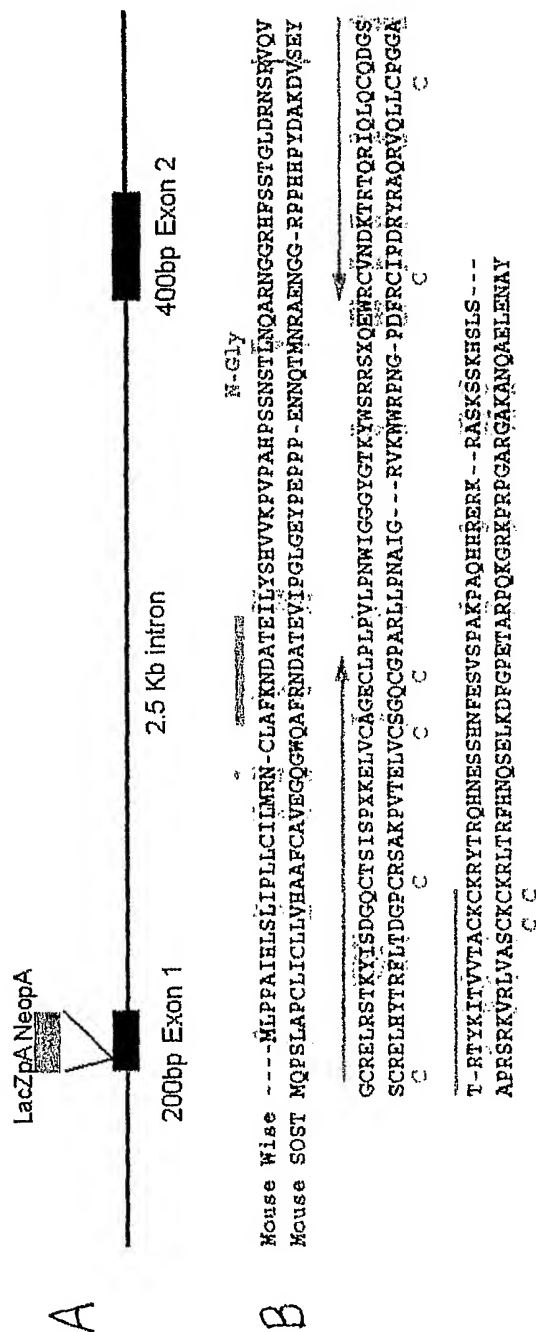


Fig. 9 A and B

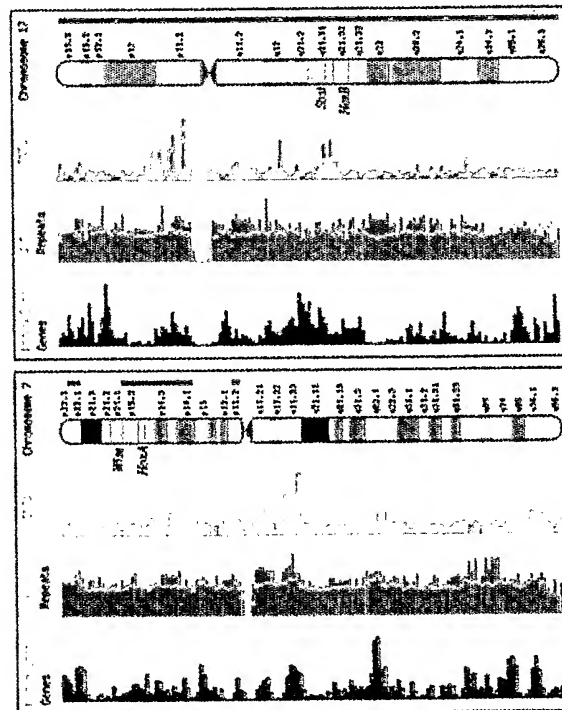
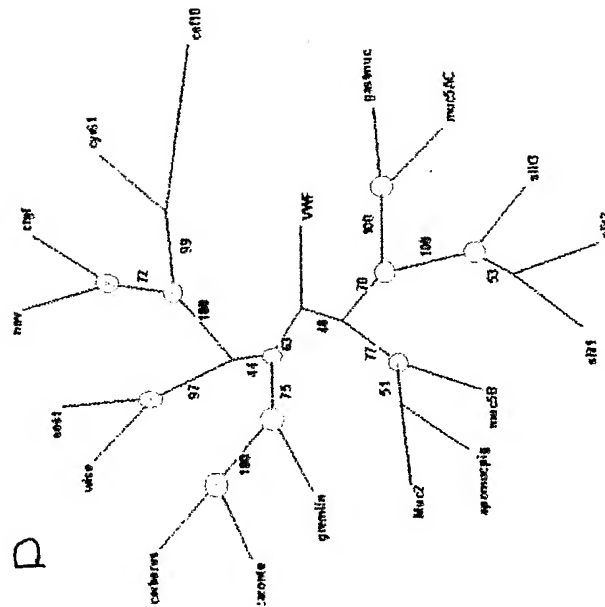


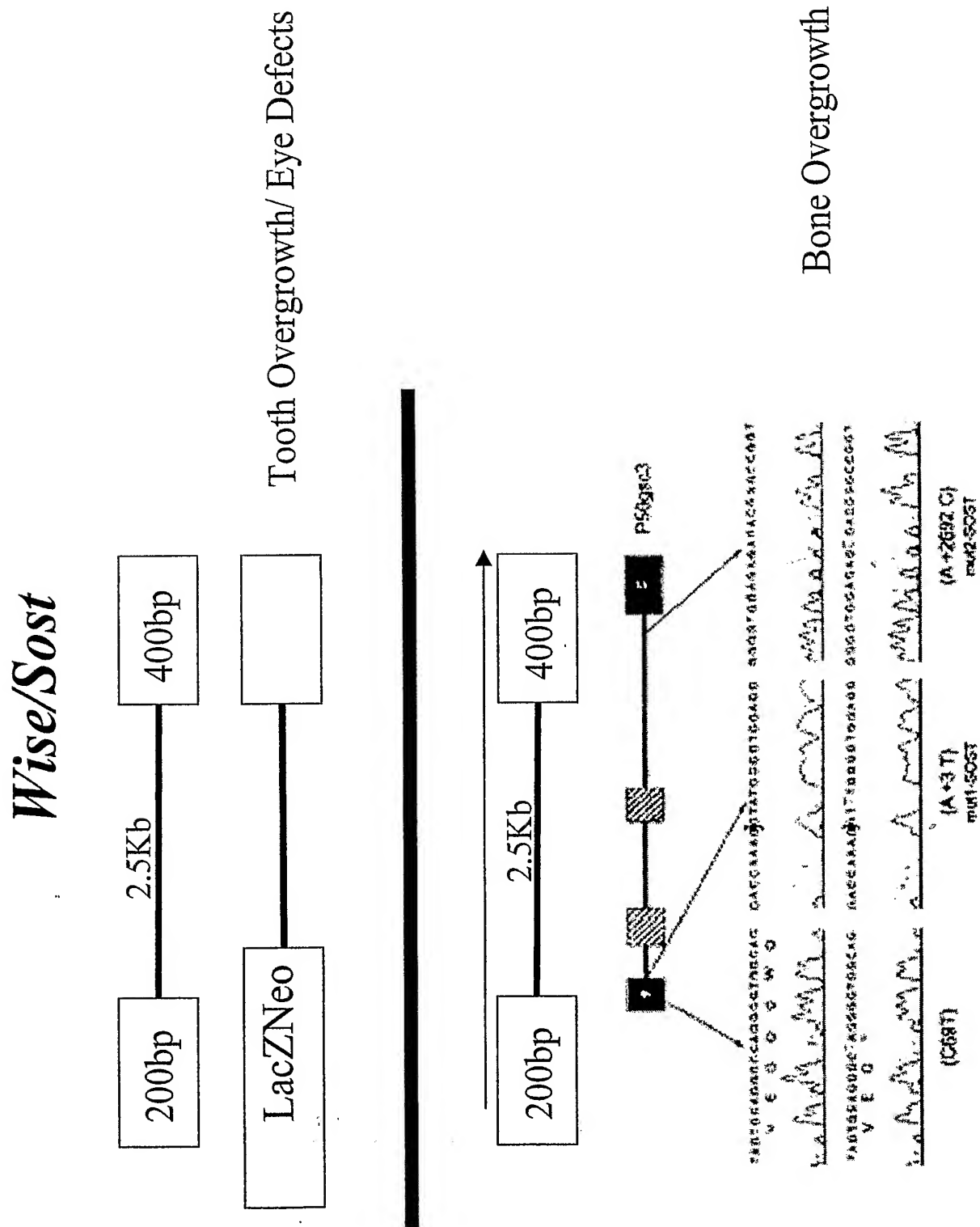
Fig 9C and D

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Fig. 9E

Fig. 10





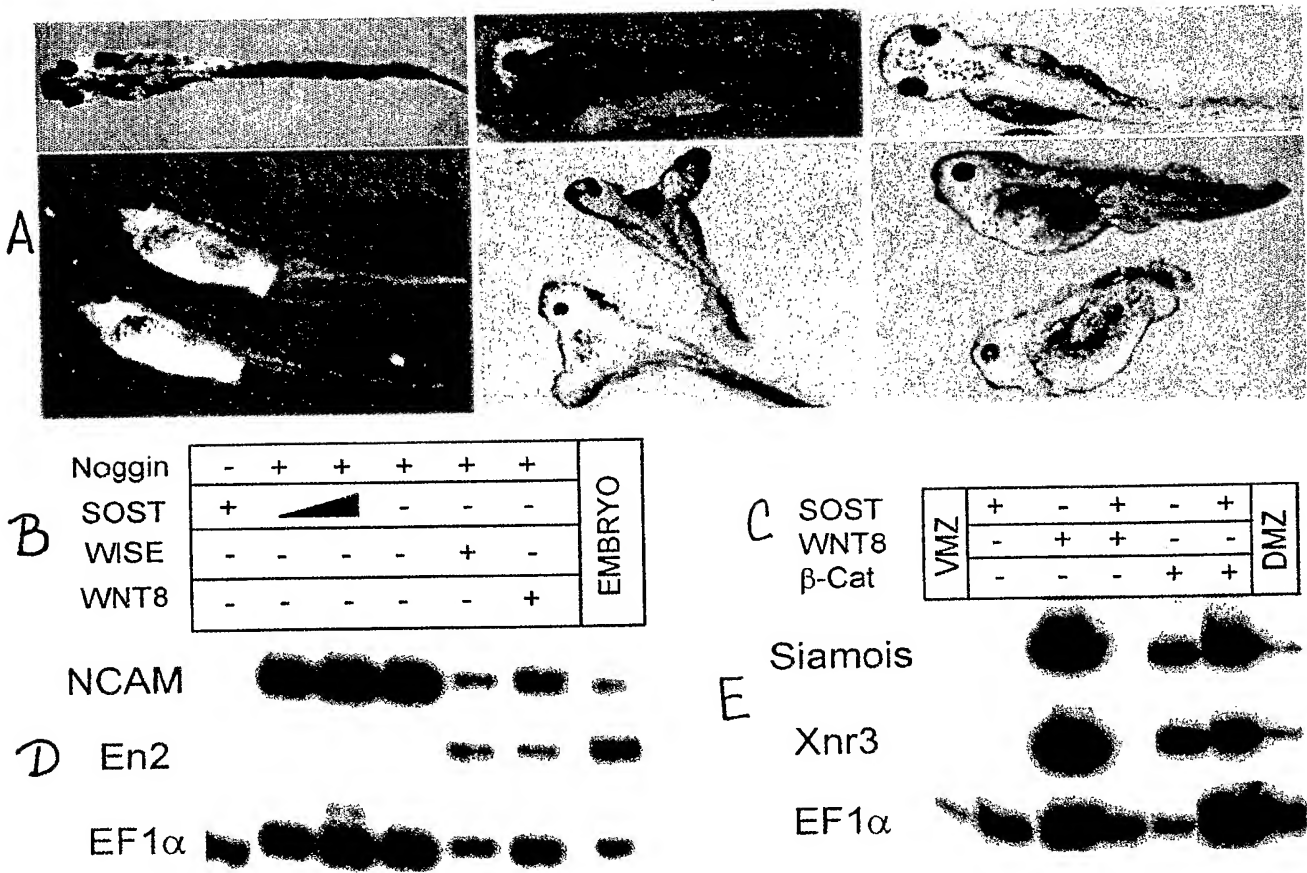


Fig. 11

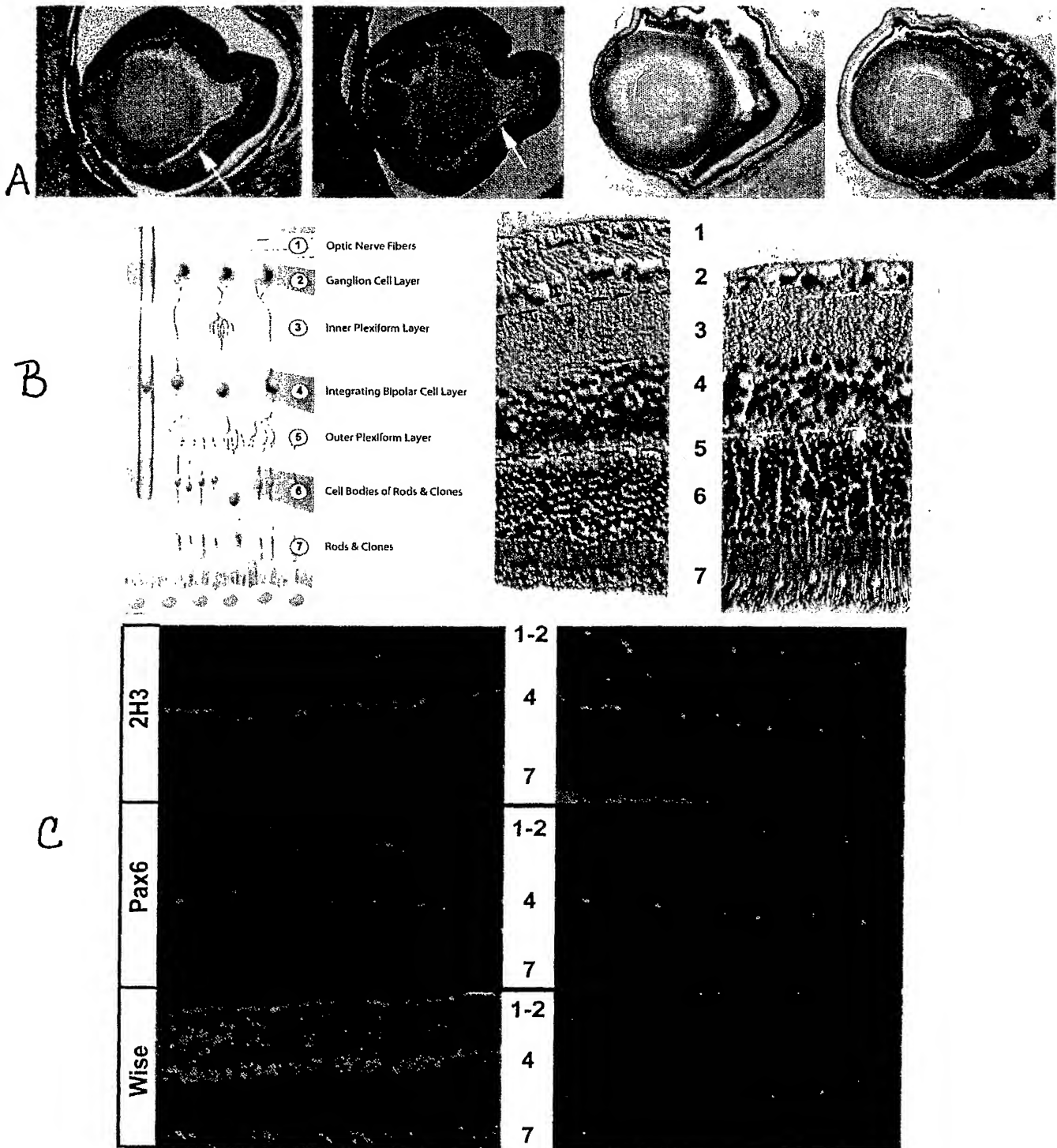


Fig. 12

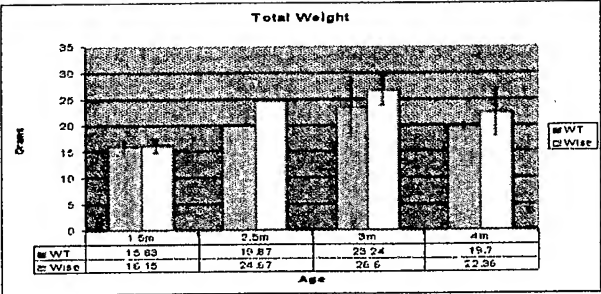
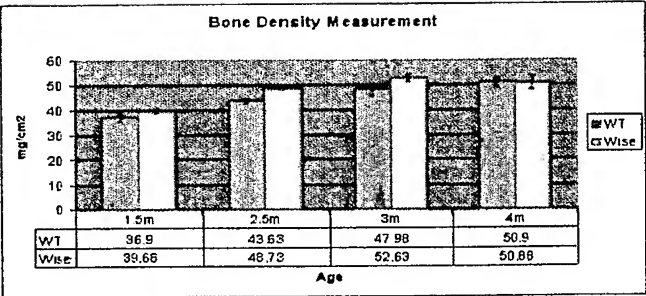
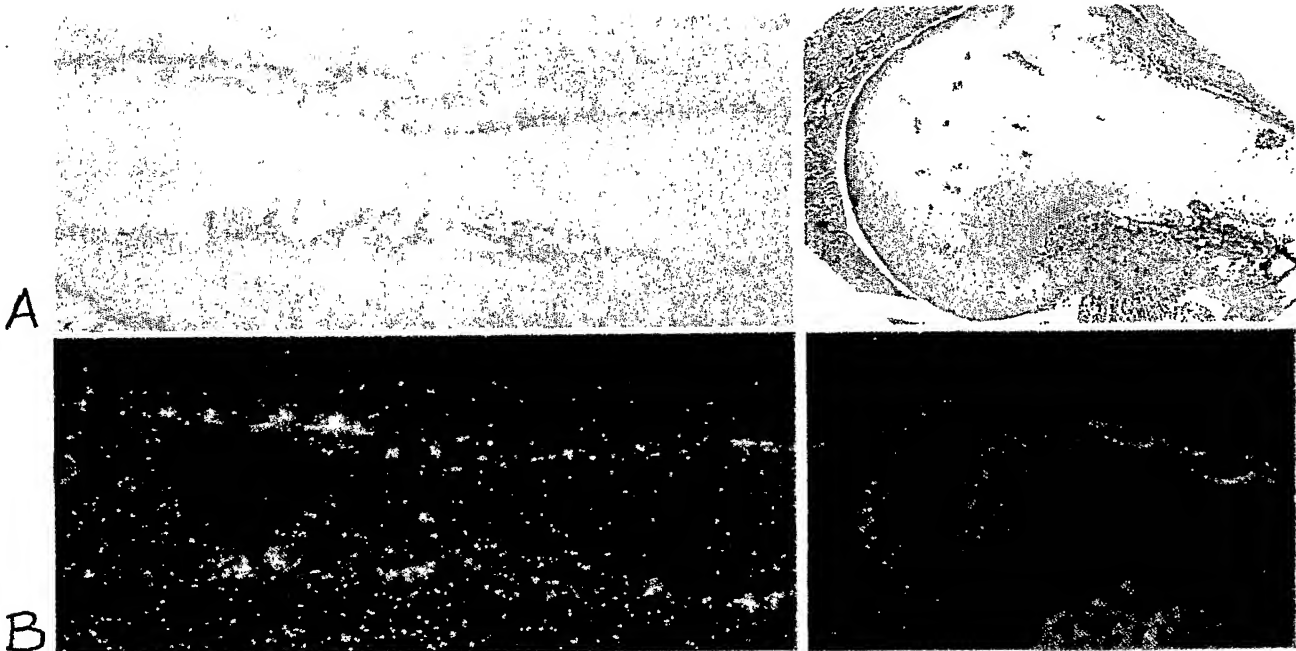


Fig. 13

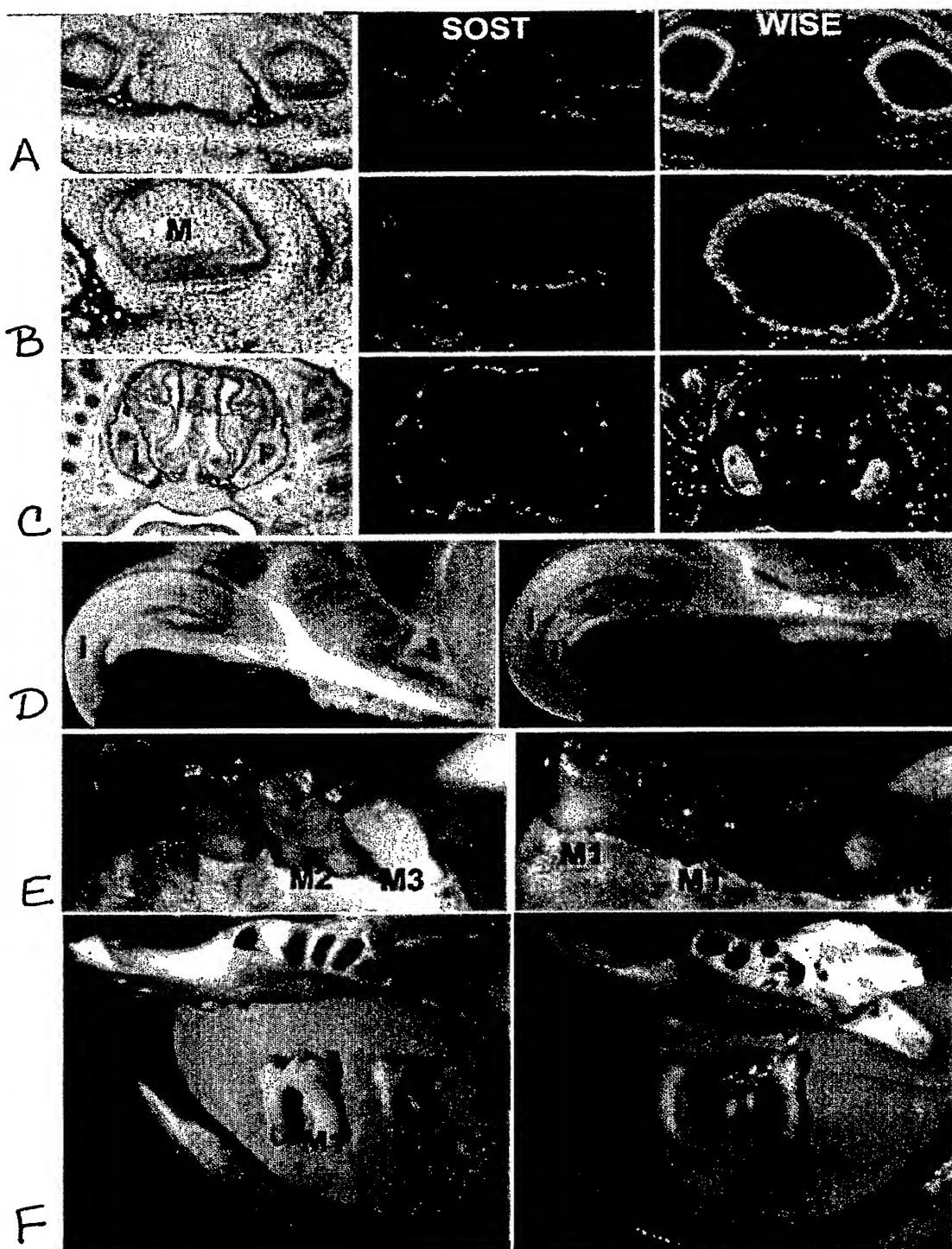


Fig. 14

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## Nonprovisional IP-017.ST25.txt

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## Nonprovisional IP-017.ST25.txt

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cctactag 3128

<210> 7  
<211> 636  
<212> DNA  
<213> MOUSE

<400> 7  
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ttggtgtgct ccggccagtg cggccccgcg cggctgtgtc ccaacgcat cgggcgcgtg 360  
aagtgggtgg gcccgaaagg accggatttc cgctgcatcc cggatcgcta ccgcgcgcag 420  
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## Nonprovisional IP-017.ST25.txt

gcctcgtgca agtgcaagcg cctcacccgc ttccacaacc agtcggagct caaggacttc 540  
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<210> 8  
 <211> 3180  
 <212> DNA  
 <213> RAT

<400> 8  
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## Nonprovisional IP-017.ST25.txt

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```

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<210> 9
<211> 675
<212> DNA
<213> MOUSE

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```

<220>
<221> misc_feature
<222> (4)..(4)
<223> n is a, c, g, or t

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```

<220>
<221> misc_feature
<222> (8)..(9)
<223> n is a, c, g, or t

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## Nonprovisional IP-017.ST25.txt

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 <221> misc\_feature  
 <222> (12)..(12)  
 <223> n is a, c, g, or t

<220>  
 <221> misc\_feature  
 <222> (19)..(19)  
 <223> n is a, c, g, or t

<220>  
 <221> misc\_feature  
 <222> (42)..(42)  
 <223> n is a, c, g, or t

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<210> 10  
 <211> 642  
 <212> DNA  
 <213> HOMO SAPIENS

<400> 10  
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 ggagagtacc ccgagcctcc accggagctg gagaacaaca agaccatgaa ccgggaggag 180  
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 gcgcagcgcg tgcagctgct gtgtcccggt ggtgaggcgc cgcgcgcgcg caaggtgcgc 480  
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## Nonprovisional IP-017.ST25.txt

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<210> 11  
 <211> 3400  
 <212> DNA  
 <213> HOMO SAPIENS

<400> 11  
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 ggagagtacc ccgagcctcc accggagctg gagaacaaca agaccatgaa ccgggcggag 180  
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## Nonprovisional IP-017.ST25.txt

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```

<210> 12
<211> 1718
<212> DNA
<213> RAT

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<400> 12
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atcctgatga aaaactgttt ggctttttaa aatgatgcca cagaaatcct ttattcacat 180

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## Nonprovisional IP-017.ST25.txt

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gtgggttaaac ctgttttcagc acaccccagc agcaacagca ccttgaatca agccaggaat 240
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```

```

<210> 13
<211> 574
<212> DNA
<213> CHICK

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<220>
<221> misc_feature
<222> (570)..(570)
<223> n is a, c, g, or t

```

```

<220>
<221> misc_feature
<222> (574)..(574)
<223> n is a, c, g, or t

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## Nonprovisional IP-017.ST25.txt

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agtcccagtc gcgggagagg aagtactcgt agtcgtcgcc gacgatcgcg ttgttcgcgg 180  
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ggatgggcag ccgtccgggc gtctggtatc cgatgttgcc ctccgtgtcg gcgtagacga 360  
ggttctgctc cggaacatcg aagaggggatg ccgcggcgcg gaagtcgtcg aagtcctggg 420  
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gcgcgtcacc ggccgccaat cccggcagcn ggn 574

<210> 14  
<211> 674  
<212> DNA  
<213> RAT

<400> 14  
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agaacgccta ctag 674

<210> 15  
<211> 1047  
<212> DNA  
<213> MOUSE

<400> 15  
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cactgccccg ccggcgtag cctgggtgctg gacggctgcg gctgctgccg cgtctgcgcc 180  
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## Nonprovisional IP-017.ST25.txt

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 tgcgaagctg acctggagga aaacattaag aaggggcaaaa agtgcacccg gacacctaaa 780  
 atcgccaagc ctgtcaagtt tgagctttct ggctgcacca gtgtgaagac atacagggtc 840  
 aagttctgcg ggggtgtgcac agacggccgc tgctgcacac cgcacagaac caccactctg 900  
 ccagtggagt tcaaatgccc cgatggcgag atcatgaaaa agaatatgat gttcatcaag 960  
 acctgtgcct gccattacaa ctgtcctggg gacaatgaca tctttgagtc cctgtactac 1020  
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<210> 16  
 <211> 1050  
 <212> DNA  
 <213> HOMO SAPIENS

<400> 16  
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 ccgcgctgcc cggcgggctg gagcctcgtg ctggacggct gcggctgctg ccgcgtctgc 180  
 gccaaagcagc tgggcgagct gtgcaccgag cgcgaccctc gcgaccgca caagggcctc 240  
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 gttcgtctgc ccagccctga ctgccccttc ccgaggaggg tcaagctgcc cgggaaatgc 480  
 tgcgaggagt ggggtgtgtga cgagcccaag gaccaaaccg tggttgggccc tgccctcgcg 540  
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 ccttgcaag ctgacctgga agagaacatt aagaaggga aaaagtgcac ccgtactccc 780  
 aaaatctcca agcctatcaa gtttgagctt tctggctgca ccagcatgaa gacataccga 840  
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 ctgccggtgg agttcaagtg ccctgacggc gaggtcatga agaagaacat gatgttcac 960  
 aagacctgtg cctgccatta caactgtccc ggagacaatg acatctttga atcgctgtac 1020

## Nonprovisional IP-017.ST25.txt

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 <211> 1050  
 <212> DNA  
 <213> BOVINE

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 aagacctgtg cctgccatta caactgccc ggagacaatg acatcttcga gtcactgtac 1020  
 tacaggaaga tgtatggaga catggcctaa 1050

<210> 18  
 <211> 1065  
 <212> DNA  
 <213> MOUSE

<400> 18  
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 ggagacaact gtgtgttcga tggggtcatt taccgcaacg gagagaagtt tgagccgaac 360  
 tgtcagtact tctgcacctg cagagatggg cagattggct gtctgccccg ctgccagcta 420  
 gacgtgctac tgccgggtcc tgactgccc gctccgagaa aagtcgcagt gccaggggag 480

## Nonprovisional IP-017.ST25.txt

tgctgcgaaa	agtggacctg	tggctcagac	gagcagggga	cacaggggac	gctgggagggc	540
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attaactgca	ttgagcagac	gacggagtgg	agcgcatgtt	ccaagagctg	tggaatgggc	660
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ttgtacacct	ataagccccg	gttctgtggg	gtctgcagtg	atggccgctg	ctgtaccccc	900
cacaacacca	aaaccatcca	ggtggagttt	cagtgtctcc	cgggggaaat	catcaagaaa	960
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<210> 19  
 <211> 1074  
 <212> DNA  
 <213> HOMO SAPIENS

<400> 19	
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ggccggtgcc	180
tgctcatgct	240
tgcgacgaga	300
atctgcacgg	360
gagaaatttc	420
gtgccccgct	480
gttgagggtgc	540
ctgggaggcc	600
gactcaagtg	660
ggtatggggg	720
actcggctct	780
ggaaaaaagt	840
tgcaccagcc	900
tgactcccc	960
gtcaagaagc	1020
aatgaggcct	1074

<210> 20  
 <211> 1140  
 <212> DNA

## Nonprovisional IP-017.ST25.txt

&lt;213&gt; MOUSE

&lt;400&gt; 20

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ccgggagtcg ggttggtccg ggacggctgc ggctgctgta aggtctgcgc taaacaactc      180
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tgcggaactg gcatctccac acgagttacc aatgacaacc cagagtgccg cctgggtgaaa      780
gagacccgga tctgtgaagt gcgtccttgt ggacaaccag tgtacagcag cctaaaaaag      840
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ttttccaaga atgtcatgat gatccagtcc tgcaaagtga actacaactg cccgcatccc     1080
aacgaggcat cgttccgact gtacagccta ttcaatgaca tccacaagtt cagggactaa     1140

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&lt;210&gt; 21

&lt;211&gt; 1146

&lt;212&gt; DNA

&lt;213&gt; HOMO SAPIENS

&lt;400&gt; 21

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ctggcgctct ccacctgccc cgctgcctgc cactgcccc caggaggcgc caagtgcgcg      120
ccgggagtcg ggctgggtccg ggacggctgc ggctgctgta aggtctgcgc caagcagctc      180
aacgaggact gcagcaaaac gcagccctgc gaccacacca aggggctgga atgcaacttc      240
ggcgccagct ccaccgctct gaaggggatc tgcagagctc agtcagaggg cagaccctgt      300
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cccaacttgg gctgtcccaa ccctcggtcgt gtcaaagtta ccgggcagtg ctgcgaggag      480
tggttctgtg acgaggatag tatcaaggac ccatggagg accaggacgg cctccttggc      540
aaggagctgg gattcgatgc ctccgaggtg gagttgacga gaaacaatga attgattgca      600

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## Nonprovisional IP-017.ST25.txt

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 aagacctgtg gaactggtat ctccacacga gttaccaatg acaaccctga gtgccgcctt 780  
 gtgaaagaaa cccggatttg tgaggtgcgg ccttgtggac agccagtgtg cagcagcctg 840  
 aaaaagggca agaaatgcag caagaccaag aaatccccg aaccagtcag gtttacttac 900  
 gctggatgtt tgagtgtgaa gaaataccgg cccaagtact gcggttcctg cgtggacggc 960  
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 gagacatttt ccaagaacgt catgatgatc cagtcctgca aatgcaacta caactgcccc 1080  
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 gactaa 1146

<210> 22  
 <211> 1140  
 <212> DNA  
 <213> RAT

<400> 22  
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 ccgggagtcg gcttgggtccg ggacggctgc ggctgctgta aggtctgcgc gaagcaactc 180  
 aacgaggact gcagcaaaac gcaaccctgc gaccacacca aggggctgga atgcaatttc 240  
 ggcgccaatt ccaccgctct gaaagggatc tgcagagctc agtcagaagg cagaccttgt 300  
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 tgcggaactg gcatctccac acgagttacc aatgacaacc cggagtgccg cctggtgaaa 780  
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 tgcacacctc tgcagaccag gaccgtgaag atgcggttcc ggtgcgaaga tggcgagatg 1020  
 ttctccaaga acgtcatgat gattcagtc tgcagtgta actacaactg cccgcatccc 1080  
 aacgaggcgt cgtttcgctt ctacagtctg ttcaacgata tccacaagtt cagggactaa 1140

<210> 23  
 <211> 1128

## Nonprovisional IP-017.ST25.txt

<212> DNA  
<213> XENOPUS

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ccaggagttg gactggttct ggatggttgt ggatgttgca aaatctgtgc taagcagctc 180  
aatgaagatt gcagcaaaac tcatccttgt gatcacacca agggacttga atgcaatttt 240  
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tgcacatgca tagatggagc tgttggttgc cttccattgt gtcctcaaga actatccctg 420  
cctaacttgg gctgccccaa tccaaggctg gtgaagggtc cagggcagtg ctgtgaggag 480  
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<210> 24  
<211> 555  
<212> DNA  
<213> MOUSE

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cacaatgact ctgagcagac ccagtcccca ccacaacctg gctccaggac ccgggggagg 180  
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tgctccttct gcaagcccaa gaagttcacc accatgatgg tcacactcaa ctgtcctgag 480  
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## Nonprovisional IP-017.ST25.txt

<210> 25  
 <211> 555  
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 <213> MOUSE

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<210> 26  
 <211> 555  
 <212> DNA  
 <213> HOMO SAPIENS

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<210> 27  
 <211> 804  
 <212> DNA  
 <213> HOMO SAPIENS

<400> 27  
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## Nonprovisional IP-017.ST25.txt

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<210> 28
<211> 804
<212> DNA
<213> HOMO SAPIENS

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gagcttccca caggcaacca tgaggaagct gaggagaagc cagatctgtt tgtcgcagtg 180
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<210> 29
<211> 13638
<212> DNA
<213> MOUSE

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<400> 29
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## Nonprovisional IP-017.ST25.txt

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## Nonprovisional IP-017.ST25.txt

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ggcctcatcc	gtgagtacat	tgtagaatac	agcaggagt	gttccaagat	gtgggcctcc	5100	
cagagggctg	ctagtaactt	tacagaaatc	aagaacttat	tgggtcaacac	tctatacacc	5160	
gtcagagtgg	ctgcggtgac	tagtcgtgga	ataggaaact	ggagcgattc	taaatccatt	5220	
accaccataa	aaggaaaagt	gatcccacca	ccagatatcc	acattgacag	ctatggtgaa	5280	
aattatctaa	gcttcaccct	gaccatggag	agtgatatca	aggatgaatgg	ctatgtggtg	5340	
aaccttttct	gggcatttga	caccacaaag	caagagagga	gaactttgaa	cttccgagga	5400	
agcatattgt	cacacaaagt	tggcaatctg	acagctcata	catcctatga	gatttctgcc	5460	
tgggccaaga	ctgacttggg	ggatagccct	ctggcatttg	agcatgttat	gaccagaggg	5520	
gttcgcccac	ctgcacctag	cctcaaggcc	aaagccatca	accagactgc	agtggaatgt	5580	
acctggaccg	gccccggaa	tgtggtttat	ggatatttct	atgccacgtc	ctttcttgac	5640	
ctctatcgca	acccgaagag	cttgactact	tcaactccaca	acaagacggg	cattgtcagt	5700	
aaggatgagc	agtatttgtt	tctgggtccgt	gtagtggtac	cctaccaggg	gccatcctct	5760	
gactacgttg	tagtgaagat	gatcccgga	agcaggcttc	caccccgta	cctgcatgtg	5820	
gttcatacgg	gcaaaacctc	cgtgggtcatc	aagtgggaat	caccgtatga	ctctcctgac	5880	

## Nonprovisional IP-017.ST25.txt

```

caggacttgt tgtatgcaat tgcagtcaaa gatctcataa gaaagactga caggagctac 5940
aaagtaaaat cccgtaacag cactgtggaa tacaccctta acaagttgga gcctggcgagg 6000
aaataccaca tcattgtcca actggggaac atgagcaaaag attccagcat aaaaattacc 6060
acagtttcat tatcagcacc tgatgcctta aaaatcataa cagaaaatga tcatgttctt 6120
ctgttttggga aaagcctggc tttaaaggaa aagcatttta atgaaagcag gggctatgag 6180
atacacatgt ttgatagtgc catgaatatac acagcttacc ttgggaatac tactgacaat 6240
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tgccttttttg gcaaccagat ctgtggggag cctgccatcc tgctgtacga tgagctgggg 6360
tctggtgcag atgcatctgc aacgcaggct gccagatcta cggatgttgc tgctgtggtg 6420
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aagcaccgga ggctgcagag cagcttcacc gccttcgcca acagccacta cagctccagg 6540
ctgggggtccg caatcttctc ctctggggat gacctggggg aagatgatga agatgccctt 6600
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```

```

<210> 45
<211> 206
<212> PRT
<213> MOUSE

```

```

<220>
<221> misc_feature
<222> (95)..(95)
<223> Xaa can be any naturally occurring amino acid

```

```

<220>
<221> misc_feature
<222> (128)..(128)
<223> Xaa can be any naturally occurring amino acid

```

```

<400> 45

```

```

Met Leu Pro Pro Ala Ile His Leu Ser Leu Ile Pro Leu Leu Cys Ile
1           5           10           15

```

```

Leu Met Arg Asn Cys Leu Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu
          20           25           30

```

```

Tyr Ser His Val Val Lys Pro Val Pro Ala His Pro Ser Ser Asn Ser
      35           40           45

```

```

Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Ser Thr Gly
 50           55           60

```

```

Leu Asp Arg Asn Ser Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser
65           70           75           80

```

```

Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Xaa Lys
          85           90           95

```



## Nonprovisional IP-017.ST25.txt

Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn  
 100 105 110  
 Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Xaa  
 115 120 125  
 Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln  
 130 135 140  
 Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val  
 145 150 155 160  
 Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser  
 165 170 175  
 His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg  
 180 185 190  
 Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser  
 195 200 205

<210> 46  
 <211> 211  
 <212> PRT  
 <213> MOUSE

<400> 46

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala  
 1 5 10 15  
 Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp  
 20 25 30  
 Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Pro Pro  
 35 40 45  
 Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro  
 50 55 60  
 His His Pro Tyr Asp Ala Lys Gly Val Ser Glu Tyr Ser Cys Arg Glu  
 65 70 75 80  
 Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys  
 85 90 95  
 Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu  
 100 105 110  
 Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro  
 115 120 125

## Nonprovisional IP-017.ST25.txt

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu  
 130 135 140  
 Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val  
 145 150 155 160  
 Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu  
 165 170 175  
 Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys  
 180 185 190  
 Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu  
 195 200 205  
 Asn Ala Tyr  
 210

<210> 47  
 <211> 211  
 <212> PRT  
 <213> MOUSE

<400> 47

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala  
 1 5 10 15  
 Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp  
 20 25 30  
 Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Pro Pro  
 35 40 45  
 Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro  
 50 55 60  
 His His Pro Tyr Asp Ala Lys Asp Val Ser Glu Tyr Ser Cys Arg Glu  
 65 70 75 80  
 Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys  
 85 90 95  
 Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu  
 100 105 110  
 Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro  
 115 120 125  
 Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu  
 130 135 140

Nonprovisional IP-017.ST25.txt

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val  
 145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu  
 165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys  
 180 185 190

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu  
 195 200 205

Asn Ala Tyr  
 210

<210> 48  
 <211> 211  
 <212> PRT  
 <213> MOUSE

<400> 48

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala  
 1 5 10 15

Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp  
 20 25 30

Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Pro Pro  
 35 40 45

Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro  
 50 55 60

His His Pro Tyr Asp Ala Lys Gly Val Ser Glu Tyr Ser Cys Arg Glu  
 65 70 75 80

Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys  
 85 90 95

Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu  
 100 105 110

Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro  
 115 120 125

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu  
 130 135 140

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val  
 145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu  
 Page 79

Nonprovisional IP-017.ST25.txt  
165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys  
180 185 190

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu  
195 200 205

Asn Ala Tyr  
210

<210> 49  
<211> 205  
<212> PRT  
<213> MOUSE

<400> 49

Met Gln Pro Ser Leu Ala Pro Cys Leu Ile Cys Leu Leu Val His Ala  
1 5 10 15

Ala Phe Cys Ala Val Glu Gly Gln Gly Trp Gln Ala Phe Arg Asn Asp  
20 25 30

Ala Thr Glu Val Ile Pro Gly Leu Gly Glu Tyr Pro Glu Pro Thr Pro  
35 40 45

Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg Pro Pro  
50 55 60

His His Pro Tyr Asp Ala Lys Asp Val Ser Glu Tyr Ser Cys Arg Glu  
65 70 75 80

Leu His Tyr Thr Arg Phe Leu Thr Asp Gly Pro Cys Arg Ser Ala Lys  
85 90 95

Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala Arg Leu  
100 105 110

Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn Gly Pro  
115 120 125

Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val Gln Leu  
130 135 140

Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val  
145 150 155 160

Ala Ser Cys Lys Cys Lys Arg Pro Thr Arg Phe His Asn Gln Ser Glu  
165 170 175

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys  
180 185 190

## Nonprovisional IP-017.ST25.txt

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala  
 195 200 205

<210> 50  
 <211> 213  
 <212> PRT  
 <213> HOMO SAPIENS  
 <400> 50

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Thr  
 1 5 10 15

Ala Phe Arg Val Val Glu Gly Gln Gly Trp Gln Ala Phe Lys Asn Asp  
 20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro  
 35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg  
 50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys  
 65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg Ser  
 85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala  
 100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser  
 115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val  
 130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala Arg Lys Val Arg  
 145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln  
 165 170 175

Ser Glu Leu Lys Asp Phe Gly Thr Glu Ala Ala Arg Pro Gln Lys Gly  
 180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu  
 195 200 205

Leu Glu Asn Ala Tyr  
 210

## Nonprovisional IP-017.ST25.txt

<210> 51  
 <211> 213  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 51

Met Gln Leu Pro Leu Ala Leu Cys Leu Val Cys Leu Leu Val His Thr  
 1 5 10 15

Ala Phe Arg Val Val Glu Gly Gln Gly Trp Gln Ala Phe Lys Asn Asp  
 20 25 30

Ala Thr Glu Ile Ile Pro Glu Leu Gly Glu Tyr Pro Glu Pro Pro Pro  
 35 40 45

Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg  
 50 55 60

Pro Pro His His Pro Phe Glu Thr Lys Gly Val Ser Glu Tyr Ser Cys  
 65 70 75 80

Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg Ser  
 85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala  
 100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser  
 115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val  
 130 135 140

Gln Leu Leu Cys Pro Gly Gly Glu Ala Pro Arg Ala Arg Lys Val Arg  
 145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln  
 165 170 175

Ser Glu Leu Lys Asp Phe Gly Thr Glu Ala Ala Arg Pro Gln Lys Gly  
 180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Ser Ala Lys Ala Asn Gln Ala Glu  
 195 200 205

Leu Glu Asn Ala Tyr  
 210

<210> 52  
 <211> 206  
 <212> PRT  
 <213> CHICK

## Nonprovisional IP-017.ST25.txt

&lt;400&gt; 52

Met Leu Leu Ser Ala Ile His Phe Tyr Gly Leu Leu Leu Ala Cys Thr  
 1 5 10 15  
 Phe Thr Arg Ser Tyr Ser Ala Phe Lys Asn Asp Ala Thr Glu Ile Leu  
 20 25 30  
 Tyr Ser His Val Val Lys Pro Ala Pro Ala Ser Pro Ser Ser Asn Ser  
 35 40 45  
 Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Tyr Ala Gly Thr Gly  
 50 55 60  
 Ser Asp Arg Asn Asn Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser  
 65 70 75 80  
 Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Asn Pro Leu Lys  
 85 90 95  
 Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Leu Leu Pro Asn  
 100 105 110  
 Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser  
 115 120 125  
 Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln  
 130 135 140  
 Leu Gln Cys Gln Asp Gly Ser Ile Arg Thr Tyr Lys Ile Thr Val Val  
 145 150 155 160  
 Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser  
 165 170 175  
 His Asn Phe Glu Gly Thr Ser Gln Ala Lys Pro Val Gln His His Lys  
 180 185 190  
 Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Thr Ser  
 195 200 205

<210> 53  
 <211> 213  
 <212> PRT  
 <213> RAT

&lt;400&gt; 53

Met Gln Leu Ser Leu Ala Pro Cys Leu Ala Cys Leu Leu Val His Ala  
 1 5 10 15  
 Ala Phe Val Ala Val Glu Ser Gln Gly Trp Gln Ala Phe Lys Asn Asp  
 20 25 30

## Nonprovisional IP-017.ST25.txt

Ala Thr Glu Ile Ile Pro Gly Leu Arg Glu Tyr Pro Glu Pro Pro Gln  
 35 40 45

Glu Leu Glu Asn Asn Gln Thr Met Asn Arg Ala Glu Asn Gly Gly Arg  
 50 55 60

Pro Pro His His Pro Tyr Asp Thr Lys Asp Val Ser Glu Tyr Ser Cys  
 65 70 75 80

Arg Glu Leu His Tyr Thr Arg Phe Val Thr Asp Gly Pro Cys Arg Ser  
 85 90 95

Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala  
 100 105 110

Arg Leu Leu Pro Asn Ala Ile Gly Arg Val Lys Trp Trp Arg Pro Asn  
 115 120 125

Gly Pro Asp Phe Arg Cys Ile Pro Asp Arg Tyr Arg Ala Gln Arg Val  
 130 135 140

Gln Leu Leu Cys Pro Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg  
 145 150 155 160

Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln  
 165 170 175

Ser Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly  
 180 185 190

Arg Lys Pro Arg Pro Arg Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu  
 195 200 205

Leu Glu Asn Ala Tyr  
 210

<210> 54  
 <211> 348  
 <212> PRT  
 <213> MOUSE

<400> 54

Met Leu Ala Ser Val Ala Gly Pro Ile Ser Leu Ala Leu Val Leu Leu  
 1 5 10 15

Ala Leu Cys Thr Arg Pro Ala Thr Gly Gln Asp Cys Ser Ala Gln Cys  
 20 25 30

Gln Cys Ala Ala Glu Ala Ala Pro His Cys Pro Ala Gly Val Ser Leu  
 35 40 45



## Nonprovisional IP-017.ST25.txt

Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu Gly  
 50 55 60  
 Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu Phe  
 65 70 75 80  
 Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr Ala  
 85 90 95  
 Lys Asp Gly Ala Pro Cys Val Phe Gly Gly Ser Val Tyr Arg Ser Gly  
 100 105 110  
 Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp Gly  
 115 120 125  
 Ala Val Gly Cys Val Pro Leu Cys Ser Met Asp Val Arg Leu Pro Ser  
 130 135 140  
 Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys Cys  
 145 150 155 160  
 Lys Glu Trp Val Cys Asp Glu Pro Lys Asp Arg Thr Ala Val Gly Pro  
 165 170 175  
 Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro Thr  
 180 185 190  
 Met Met Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala Cys  
 195 200 205  
 Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp Asn  
 210 215 220  
 Thr Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg Pro  
 225 230 235 240  
 Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys Ile  
 245 250 255  
 Arg Thr Pro Lys Ile Ala Lys Pro Val Lys Phe Glu Leu Ser Gly Cys  
 260 265 270  
 Thr Ser Val Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr Asp  
 275 280 285  
 Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu Phe  
 290 295 300  
 Lys Cys Pro Asp Gly Glu Ile Met Lys Lys Asn Met Met Phe Ile Lys  
 305 310 315 320

## Nonprovisional IP-017.ST25.txt

Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe Glu  
 325 330 335

Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala  
 340 345

<210> 55  
 <211> 349  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 55

Met Thr Ala Ala Ser Met Gly Pro Val Arg Val Ala Phe Val Val Leu  
 1 5 10 15

Leu Ala Leu Cys Ser Arg Pro Ala Val Gly Gln Asn Cys Ser Gly Pro  
 20 25 30

Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser  
 35 40 45

Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu  
 50 55 60

Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu  
 65 70 75 80

Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr  
 85 90 95

Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser  
 100 105 110

Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp  
 115 120 125

Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro  
 130 135 140

Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys  
 145 150 155 160

Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly  
 165 170 175

Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro  
 180 185 190

Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala  
 195 200 205

## Nonprovisional IP-017.ST25.txt

Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp  
 210 215 220

Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg  
 225 230 235 240

Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys  
 245 250 255

Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly  
 260 265 270

Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr  
 275 280 285

Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu  
 290 295 300

Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile  
 305 310 315 320

Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe  
 325 330 335

Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala  
 340 345

<210> 56

<211> 347

<212> PRT

<213> RAT

<400> 56

Met Leu Ala Ser Val Ala Gly Pro Val Ser Leu Ala Leu Val Leu Leu  
 1 5 10 15

Leu Cys Thr Arg Pro Ala Thr Gly Gln Asp Cys Ser Ala Gln Cys Gln  
 20 25 30

Cys Ala Ala Glu Ala Ala Pro Arg Cys Pro Ala Gly Val Ser Leu Val  
 35 40 45

Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu Gly Glu  
 50 55 60

Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu Phe Cys  
 65 70 75 80

Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr Ala Lys  
 85 90 95

Asp Gly Ala Pro Cys Val Phe Gly Gly Ser Val Tyr Arg Ser Gly Glu  
 Page 87

Nonprovisional IP-017.ST25.txt

100

105

110

Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp Gly Ala  
 115 120 125  
 Val Gly Cys Val Pro Leu Cys Ser Met Asp Val Arg Leu Pro Ser Pro  
 130 135 140  
 Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys Cys Glu  
 145 150 155 160  
 Glu Trp Val Cys Asp Glu Pro Lys Asp Arg Thr Val Val Gly Pro Ala  
 165 170 175  
 Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro Thr Met  
 180 185 190  
 Met Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala Cys Ser  
 195 200 205  
 Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Thr  
 210 215 220  
 Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg Pro Cys  
 225 230 235 240  
 Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys Ile Arg  
 245 250 255  
 Thr Pro Lys Ile Ala Lys Pro Val Lys Phe Glu Leu Ser Gly Cys Thr  
 260 265 270  
 Ser Val Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr Asp Gly  
 275 280 285  
 Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu Phe Lys  
 290 295 300  
 Cys Pro Asp Gly Glu Ile Met Lys Lys Asn Met Met Phe Ile Lys Thr  
 305 310 315 320  
 Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe Glu Ser  
 325 330 335  
 Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala  
 340 345

<210> 57  
 <211> 349  
 <212> PRT  
 <213> BOVINE

## Nonprovisional IP-017.ST25.txt

&lt;400&gt; 57

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Met Ser Ala Thr Gly Leu Gly Pro Val Arg Cys Ala Phe Val Leu Leu
1      5      10      15

Leu Ala Leu Cys Ser Arg Pro Ala Ser Ser Gln Asp Cys Cys Ser Ala
20      25      30

Pro Cys Gln Cys Pro Ala Gly Pro Ala Pro Arg Cys Pro Ala Gly Val
35      40      45

Ser Leu Val Leu Asp Gly Cys Gly Cys Cys Val Cys Ala Lys Gln Leu
50      55      60

Ser Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65      70      75      80

Phe Cys Asp Phe Gly Ser Pro Thr Asn Arg Lys Ile Gly Val Cys Thr
85      90      95

Ala Lys Asp Gly Ala Pro Tyr Ile Phe Gly Gly Thr Val Tyr Gln Ser
100     105     110

Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
115     120     125

Gly Ser Val Gly Cys Val Pro Leu Cys Ser Val Asp Val Arg Leu Pro
130     135     140

Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
145     150     155     160

Cys Glu Glu Trp Val Ser Arg Asp Glu Lys Glu His Thr Val Val Gly
165     170     175

Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
180     185     190

Thr Met Ile Arg Ala Asn Cys Gln Val Gln Thr Thr Glu Trp Ser Ala
195     200     205

Tyr Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
210     215     220

Asn Ala Phe Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225     230     235     240

Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245     250     255

Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Gln Leu Ser Gly
260     265     270

```

## Nonprovisional IP-017.ST25.txt

Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Phe Gly Val Cys Thr  
 275 280 285

Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu  
 290 295 300

Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Ser Met Met Phe Ile  
 305 310 315 320

Lys Thr Cys Ala Cys His Tyr Asn Cys Pro Gly Asp Asn Asp Ile Phe  
 325 330 335

Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala  
 340 345

<210> 58  
 <211> 354  
 <212> PRT  
 <213> MOUSE

<400> 58

Met Ser Leu Phe Leu Arg Lys Arg Cys Leu Cys Leu Gly Phe Leu Leu  
 1 5 10 15

Phe His Leu Leu Ser Gln Val Ser Ala Ser Leu Arg Cys Pro Ser Arg  
 20 25 30

Cys Pro Pro Lys Cys Pro Ser Ile Ser Pro Thr Cys Ala Pro Gly Val  
 35 40 45

Arg Ser Val Leu Asp Gly Cys Ser Cys Cys Pro Val Cys Ala Arg Gln  
 50 55 60

Arg Gly Glu Ser Cys Ser Glu Met Arg Pro Cys Asp Gln Ser Ser Gly  
 65 70 75 80

Leu Tyr Cys Asp Arg Ser Ala Asp Pro Asn Asn Gln Thr Gly Ile Cys  
 85 90 95

Met Val Pro Glu Gly Asp Asn Cys Val Phe Asp Gly Val Ile Tyr Arg  
 100 105 110

Asn Gly Glu Lys Phe Glu Pro Asn Cys Gln Tyr Phe Cys Thr Cys Arg  
 115 120 125

Asp Gly Gln Ile Gly Cys Leu Pro Arg Cys Gln Leu Asp Val Leu Leu  
 130 135 140

Pro Gly Pro Asp Cys Pro Ala Pro Arg Lys Val Ala Val Pro Gly Glu  
 145 150 155 160

## Nonprovisional IP-017.ST25.txt

Cys Cys Glu Lys Trp Thr Cys Gly Ser Asp Glu Gln Gly Thr Gln Gly  
 165 170 175  
 Thr Leu Gly Gly Leu Ala Leu Pro Ala Tyr Arg Pro Glu Ala Thr Val  
 180 185 190  
 Gly Val Glu Val Ser Asp Ser Ser Ile Asn Cys Ile Glu Gln Thr Thr  
 195 200 205  
 Glu Trp Ser Ala Cys Ser Lys Ser Cys Gly Met Gly Val Ser Thr Arg  
 210 215 220  
 Val Thr Asn Arg Asn Arg Gln Cys Glu Met Val Lys Gln Thr Arg Leu  
 225 230 235 240  
 Cys Ile Val Arg Pro Cys Glu Gln Glu Pro Glu Glu Val Thr Asp Lys  
 245 250 255  
 Lys Gly Lys Lys Cys Leu Arg Thr Lys Lys Ser Leu Lys Ala Ile His  
 260 265 270  
 Leu Gln Phe Glu Asn Cys Thr Ser Leu Tyr Thr Tyr Lys Pro Arg Phe  
 275 280 285  
 Cys Gly Val Cys Ser Asp Gly Arg Cys Cys Thr Pro His Asn Thr Lys  
 290 295 300  
 Thr Ile Gln Val Glu Phe Gln Cys Leu Pro Gly Glu Ile Ile Lys Lys  
 305 310 315 320  
 Pro Val Met Val Ile Gly Thr Cys Thr Cys Tyr Ser Asn Cys Pro Gln  
 325 330 335  
 Asn Asn Glu Ala Phe Leu Gln Asp Leu Glu Leu Lys Thr Ser Arg Gly  
 340 345 350

Glu Ile

<210> 59  
 <211> 357  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 59

Met Gln Ser Val Gln Ser Thr Ser Phe Cys Leu Arg Lys Gln Cys Leu  
 1 5 10 15  
 Cys Leu Thr Phe Leu Leu Leu His Leu Leu Gly Gln Val Ala Ala Thr  
 20 25 30

Nonprovisional IP-017.ST25.txt

Gln Arg Cys Pro Pro Gln Cys Pro Gly Arg Cys Pro Ala Thr Pro Pro  
 35 40 45

Thr Cys Ala Pro Gly Val Arg Ala Val Leu Asp Gly Cys Ser Cys Cys  
 50 55 60

Leu Val Cys Ala Arg Gln Arg Gly Glu Ser Cys Ser Asp Leu Glu Pro  
 65 70 75 80

Cys Asp Glu Ser Ser Gly Leu Tyr Cys Asp Arg Ser Ala Asp Pro Ser  
 85 90 95

Asn Gln Thr Gly Ile Cys Thr Ala Val Glu Gly Asp Asn Cys Val Phe  
 100 105 110

Asp Gly Val Ile Tyr Arg Ser Gly Glu Lys Phe Gln Pro Ser Cys Lys  
 115 120 125

Phe Gln Cys Thr Cys Arg Asp Gly Gln Ile Gly Cys Val Pro Arg Cys  
 130 135 140

Gln Leu Asp Val Leu Leu Pro Glu Pro Asn Cys Pro Ala Pro Arg Lys  
 145 150 155 160

Val Glu Val Pro Gly Glu Cys Cys Glu Lys Trp Ile Cys Gly Pro Asp  
 165 170 175

Glu Glu Asp Ser Leu Gly Gly Leu Thr Leu Ala Ala Tyr Arg Pro Glu  
 180 185 190

Ala Thr Leu Gly Val Glu Val Ser Asp Ser Ser Val Asn Cys Ile Glu  
 195 200 205

Gln Thr Thr Glu Trp Thr Ala Cys Ser Lys Ser Cys Gly Met Gly Phe  
 210 215 220

Ser Thr Arg Val Thr Asn Arg Asn Arg Gln Cys Glu Met Leu Lys Gln  
 225 230 235 240

Thr Arg Leu Cys Met Val Arg Pro Cys Glu Gln Glu Pro Glu Gln Pro  
 245 250 255

Thr Asp Lys Lys Gly Lys Lys Cys Leu Arg Thr Lys Lys Ser Leu Lys  
 260 265 270

Ala Ile His Leu Gln Phe Lys Asn Cys Thr Ser Leu His Thr Tyr Lys  
 275 280 285

Pro Arg Phe Cys Gly Val Cys Ser Asp Gly Arg Cys Cys Thr Pro His  
 290 295 300



## Nonprovisional IP-017.ST25.txt

Asn Thr Lys Thr Ile Gln Ala Glu Phe Gln Cys Ser Pro Gly Gln Ile  
 305 310 315 320

Val Lys Lys Pro Val Met Val Ile Gly Thr Cys Thr Cys His Thr Asn  
 325 330 335

Cys Pro Lys Asn Asn Glu Ala Phe Leu Gln Glu Leu Glu Leu Lys Thr  
 340 345 350

Thr Arg Gly Lys Met  
 355

<210> 60  
 <211> 379  
 <212> PRT  
 <213> MOUSE

<400> 60

Met Ser Ser Ser Thr Phe Arg Thr Leu Ala Val Ala Val Thr Leu Leu  
 1 5 10 15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His Cys  
 20 25 30

Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp  
 35 40 45

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys  
 50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe  
 65 70 75 80

Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu  
 85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Arg Ile Tyr Gln Asn Gly Glu Ser  
 100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val  
 115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly  
 130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Ser Gly Gln Cys Cys Glu Glu  
 145 150 155 160

Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Ser Leu Asp Asp Gln Asp  
 165 170 175

Asp Leu Leu Gly Leu Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn

## Nonprovisional IP-017.ST25.txt

180

185

190

Glu Leu Ile Ala Ile Gly Lys Gly Ser Ser Leu Lys Arg Leu Pro Val  
 195 200 205

Phe Gly Thr Glu Pro Arg Val Leu Phe Asn Pro Leu His Ala His Gly  
 210 215 220

Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys Ser  
 225 230 235 240

Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro Glu Cys  
 245 250 255

Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln  
 260 265 270

Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys  
 275 280 285

Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val  
 290 295 300

Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys  
 305 310 315 320

Cys Thr Pro Leu Gln Thr Arg Thr Val Lys Met Arg Phe Arg Cys Glu  
 325 330 335

Asp Gly Glu Met Phe Ser Lys Asn Val Met Met Ile Gln Ser Cys Lys  
 340 345 350

Cys Asn Tyr Asn Cys Pro His Pro Asn Glu Ala Ser Phe Arg Leu Tyr  
 355 360 365

Ser Leu Phe Asn Asp Ile His Lys Phe Arg Asp  
 370 375

<210> 61  
 <211> 381  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 61

Met Ser Ser Arg Ile Ala Arg Ala Leu Ala Leu Val Val Thr Leu Leu  
 1 5 10 15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ala Cys His Cys  
 20 25 30

Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp  
 35 40 45

## Nonprovisional IP-017.ST25.txt

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys  
 50 55 60  
 Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe  
 65 70 75 80  
 Gly Ala Ser Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu  
 85 90 95  
 Gly Arg Pro Cys Glu Tyr Asn Ser Arg Ile Tyr Gln Asn Gly Glu Ser  
 100 105 110  
 Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val  
 115 120 125  
 Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly  
 130 135 140  
 Cys Pro Asn Pro Arg Leu Val Lys Val Thr Gly Gln Cys Cys Glu Glu  
 145 150 155 160  
 Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Pro Met Glu Asp Gln Asp  
 165 170 175  
 Gly Leu Leu Gly Lys Glu Leu Gly Phe Asp Ala Ser Glu Val Glu Leu  
 180 185 190  
 Thr Arg Asn Asn Glu Leu Ile Ala Val Gly Lys Gly Ser Ser Leu Lys  
 195 200 205  
 Arg Leu Pro Val Phe Gly Met Glu Pro Arg Ile Leu Tyr Asn Pro Leu  
 210 215 220  
 Gln Gly Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser  
 225 230 235 240  
 Lys Thr Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro  
 245 250 255  
 Glu Cys Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys  
 260 265 270  
 Gly Gln Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys  
 275 280 285  
 Thr Lys Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Leu  
 290 295 300  
 Ser Val Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly  
 305 310 315 320

## Nonprovisional IP-017.ST25.txt

Arg Cys Cys Thr Pro Gln Leu Thr Arg Thr Val Lys Met Arg Phe Arg  
325 330 335

Cys Glu Asp Gly Glu Thr Phe Ser Lys Asn Val Met Met Ile Gln Ser  
340 345 350

Cys Lys Cys Asn Tyr Asn Cys Pro His Ala Asn Glu Ala Ala Phe Pro  
355 360 365

Phe Tyr Arg Leu Phe Asn Asp Ile His Lys Phe Arg Asp  
370 375 380

<210> 62

<211> 379

<212> PRT

<213> RAT

<400> 62

Met Ser Ser Ser Thr Ile Lys Thr Leu Ala Val Ala Val Thr Leu Leu  
1 5 10 15

His Leu Thr Arg Leu Ala Leu Ser Thr Cys Pro Ala Ser Cys His Cys  
20 25 30

Pro Leu Glu Ala Pro Lys Cys Ala Pro Gly Val Gly Leu Val Arg Asp  
35 40 45

Gly Cys Gly Cys Cys Lys Val Cys Ala Lys Gln Leu Asn Glu Asp Cys  
50 55 60

Ser Lys Thr Gln Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe  
65 70 75 80

Gly Ala Asn Ser Thr Ala Leu Lys Gly Ile Cys Arg Ala Gln Ser Glu  
85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Arg Ile Tyr Gln Asn Gly Glu Ser  
100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val  
115 120 125

Gly Cys Ile Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly  
130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Ser Gly Gln Cys Cys Glu Glu  
145 150 155 160

Trp Val Cys Asp Glu Asp Ser Ile Lys Asp Ser Leu Asp Asp Gln Asp  
165 170 175

## Nonprovisional IP-017.ST25.txt

Asp Leu Leu Gly Phe Asp Ala Ser Glu Val Glu Leu Thr Arg Asn Asn  
 180 185 190  
 Glu Leu Ile Ala Thr Gly Lys Gly Ser Ser Leu Lys Arg Leu Pro Val  
 195 200 205  
 Phe Gly Thr Glu Pro Arg Val Leu Tyr Asn Pro Leu His Ala His Gly  
 210 215 220  
 Gln Lys Cys Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys Ser  
 225 230 235 240  
 Cys Gly Thr Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Pro Glu Cys  
 245 250 255  
 Arg Leu Val Lys Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln  
 260 265 270  
 Pro Val Tyr Ser Ser Leu Lys Lys Gly Lys Lys Cys Ser Lys Thr Lys  
 275 280 285  
 Lys Ser Pro Glu Pro Val Arg Phe Thr Tyr Ala Gly Cys Ser Ser Val  
 290 295 300  
 Lys Lys Tyr Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys  
 305 310 315 320  
 Cys Thr Pro Leu Gln Thr Arg Thr Val Lys Met Arg Phe Arg Cys Glu  
 325 330 335  
 Asp Gly Glu Met Phe Ser Lys Asn Val Met Met Ile Gln Ser Cys Lys  
 340 345 350  
 Cys Asn Tyr Asn Cys Pro His Pro Asn Glu Ala Ser Phe Arg Leu Tyr  
 355 360 365  
 Ser Leu Phe Asn Asp Ile His Lys Phe Arg Asp  
 370 375  
 <210> 63  
 <211> 375  
 <212> PRT  
 <213> XENOPUS  
 <400> 63  
 Met Ser Phe Leu Ala Leu Asn Pro Val Leu Ala Ile Ala Leu Leu Ser  
 1 5 10 15  
 Gly Phe Ile Asp Leu Ala Val Ser Ser Cys Pro Ala Val Cys Gln Cys  
 20 25 30

Nonprovisional IP-017.ST25.txt

Pro Val Glu Val Pro Lys Cys Ala Pro Gly Val Gly Leu Val Leu Asp  
 35 40 45

Gly Cys Gly Cys Cys Lys Ile Cys Ala Lys Gln Leu Asn Glu Asp Cys  
 50 55 60

Ser Lys Thr His Pro Cys Asp His Thr Lys Gly Leu Glu Cys Asn Phe  
 65 70 75 80

Gly Ala Ser Ser Arg Ala Ile Lys Gly Ile Cys Arg Ala Lys Ser Glu  
 85 90 95

Gly Arg Pro Cys Glu Tyr Asn Ser Lys Ile Tyr Gln Asn Gly Glu Ser  
 100 105 110

Phe Gln Pro Asn Cys Lys His Gln Cys Thr Cys Ile Asp Gly Ala Val  
 115 120 125

Gly Cys Leu Pro Leu Cys Pro Gln Glu Leu Ser Leu Pro Asn Leu Gly  
 130 135 140

Cys Pro Asn Pro Arg Leu Val Lys Val Pro Gly Gln Cys Cys Glu Glu  
 145 150 155 160

Trp Val Cys Asp Glu Ala Lys Asp Pro Val Asp Glu Met Asp Asp Phe  
 165 170 175

Phe Asn Lys Glu Phe Gly Met Asp Thr Asn Glu Gly Glu Leu Thr Arg  
 180 185 190

Lys Asn Glu Phe Val Ala Val Ile Lys Gly Gly Leu Lys Met Leu Pro  
 195 200 205

Val Phe Gly Ser Asp Pro Gln Ser His Val Val Glu Asn Ser Lys Cys  
 210 215 220

Ile Val Gln Thr Thr Ser Trp Ser Gln Cys Ser Lys Thr Cys Gly Thr  
 225 230 235 240

Gly Ile Ser Thr Arg Val Thr Asn Asp Asn Ser Asn Cys Arg Leu Val  
 245 250 255

Arg Glu Thr Arg Ile Cys Glu Val Arg Pro Cys Gly Gln Pro Ser Tyr  
 260 265 270

Thr Ser Leu Lys Lys Gly Lys Lys Cys Thr Lys Thr Lys Lys Ser Gln  
 275 280 285

Ala Pro Val Arg Tyr Thr Tyr Ala Gly Cys Ser Ser Val Lys Lys Tyr  
 290 295 300

Nonprovisional IP-017.ST25.txt

Arg Pro Lys Tyr Cys Gly Ser Cys Val Asp Gly Arg Cys Cys Thr Pro  
 305 310 315 320

Gln Gln Thr Arg Thr Val Lys Ile Arg Phe Arg Cys Glu Asp Gly Glu  
 325 330 335

Thr Phe Thr Lys Asn Val Met Met Ile Gln Ser Cys Arg Cys Asn Tyr  
 340 345 350

Asn Cys Pro His Thr Asn Glu Ala Tyr Pro Tyr Tyr Arg Leu Phe Asn  
 355 360 365

Asp Ile His Lys Phe Arg Asp  
 370 375

<210> 64  
 <211> 184  
 <212> PRT  
 <213> MOUSE

<400> 64

Met Asn Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly  
 1 5 10 15

Thr Leu Leu Pro Thr Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala  
 20 25 30

Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln  
 35 40 45

Ser Pro Pro Gln Pro Gly Ser Arg Thr Arg Gly Arg Gly Gln Gly Arg  
 50 55 60

Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala  
 65 70 75 80

Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr  
 85 90 95

Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr  
 100 105 110

Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro  
 115 120 125

Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys  
 130 135 140

Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu  
 145 150 155 160

Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys  
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Nonprovisional IP-017.ST25.txt  
170

165

175

Arg Cys Ile Ser Ile Asp Leu Asp  
180<210> 65  
<211> 184  
<212> PRT  
<213> MOUSE  
<400> 65Met Asn Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Gly  
1 5 10 15Thr Leu Leu Pro Thr Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala  
20 25 30Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln  
35 40 45Ser Pro Pro Gln Pro Gly Ser Arg Thr Arg Gly Arg Gly Gln Gly Arg  
50 55 60Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala  
65 70 75 80Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr  
85 90 95Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr  
100 105 110Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro  
115 120 125Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys  
130 135 140Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu  
145 150 155 160Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys  
165 170 175Arg Cys Ile Ser Ile Asp Leu Asp  
180<210> 66  
<211> 184  
<212> PRT  
<213> HOMO SAPIENS  
<400> 66



## Nonprovisional IP-017.ST25.txt

Met Ser Arg Thr Ala Tyr Thr Val Gly Ala Leu Leu Leu Leu Leu Gly  
 1 5 10 15  
 Thr Leu Leu Pro Ala Ala Glu Gly Lys Lys Lys Gly Ser Gln Gly Ala  
 20 25 30  
 Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln  
 35 40 45  
 Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg  
 50 55 60  
 Gly Thr Ala Met Pro Gly Glu Glu Val Leu Glu Ser Ser Gln Glu Ala  
 65 70 75 80  
 Leu His Val Thr Glu Arg Lys Tyr Leu Lys Arg Asp Trp Cys Lys Thr  
 85 90 95  
 Gln Pro Leu Lys Gln Thr Ile His Glu Glu Gly Cys Asn Ser Arg Thr  
 100 105 110  
 Ile Ile Asn Arg Phe Cys Tyr Gly Gln Cys Asn Ser Phe Tyr Ile Pro  
 115 120 125  
 Arg His Ile Arg Lys Glu Glu Gly Ser Phe Gln Ser Cys Ser Phe Cys  
 130 135 140  
 Lys Pro Lys Lys Phe Thr Thr Met Met Val Thr Leu Asn Cys Pro Glu  
 145 150 155 160  
 Leu Gln Pro Pro Thr Lys Lys Lys Arg Val Thr Arg Val Lys Gln Cys  
 165 170 175  
 Arg Cys Ile Ser Ile Asp Leu Asp  
 180

<210> 67  
 <211> 4545  
 <212> PRT  
 <213> MOUSE

<400> 67

Met Leu Thr Pro Pro Leu Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu  
 1 5 10 15  
 Val Ser Gly Ala Thr Met Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln  
 20 25 30  
 Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys  
 35 40 45

Nonprovisional IP-017.ST25.txt

Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile  
 50 55 60

Cys Pro Gln Ser Lys Ala Gln Arg Cys Pro Pro Asn Glu His Ser Cys  
 65 70 75 80

Leu Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Ile  
 85 90 95

Gln Asp Cys Met Asp Gly Ser Asp Glu Gly Ala His Cys Arg Glu Leu  
 100 105 110

Arg Ala Asn Cys Ser Arg Met Gly Cys Gln His His Cys Val Pro Thr  
 115 120 125

Pro Ser Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala  
 130 135 140

Asp Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr  
 145 150 155 160

Cys Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Thr Cys Gly Cys  
 165 170 175

Val Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys  
 180 185 190

Asn Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln  
 195 200 205

Asn Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr  
 210 215 220

Pro Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn  
 225 230 235 240

Glu Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln  
 245 250 255

Leu Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His  
 260 265 270

Thr Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile  
 275 280 285

Asp Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg  
 290 295 300

Ile Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp  
 305 310 315 320

Nonprovisional IP-017.ST25.txt

Leu Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly  
 325 330 335

Lys Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys  
 340 345 350

Asp Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val  
 355 360 365

Phe Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp  
 370 375 380

Ala Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys  
 385 390 395 400

Gly Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly  
 405 410 415

Leu Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala  
 420 425 430

Asn Thr Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser  
 435 440 445

Thr Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His  
 450 455 460

Ile Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu  
 465 470 475 480

Asn Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu  
 485 490 495

Ala Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser  
 500 505 510

Leu Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe  
 515 520 525

Leu Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met  
 530 535 540

Gly Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met  
 545 550 555 560

Asn Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe  
 565 570 575

Ala Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr  
 580 585 590

Nonprovisional IP-017.ST25.txt

Glu Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val  
595 600 605

Ala Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro  
610 615 620

Lys Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg  
625 630 635 640

Lys Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val  
645 650 655

Asp Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro  
660 665 670

Lys Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser  
675 680 685

His Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly  
690 695 700

Leu Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe  
705 710 715 720

Tyr Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile  
725 730 735

Val Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His  
740 745 750

Gly Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg  
755 760 765

Leu Glu Arg Gly Val Ala Gly Ala Pro Pro Thr Val Thr Leu Leu Arg  
770 775 780

Ser Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln  
785 790 795 800

Gln Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser  
805 810 815

Ser Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu  
820 825 830

Asp Gln Val Leu Asp Thr Asp Gly Val Thr Cys Leu Ala Asn Pro Ser  
835 840 845

Tyr Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn  
850 855 860

## Nonprovisional IP-017.ST25.txt

Asn Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys  
 865 870 875 880  
 Leu Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys  
 885 890 895  
 Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg  
 900 905 910  
 Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser  
 915 920 925  
 Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys  
 930 935 940  
 Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp  
 945 950 955 960  
 Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr  
 965 970 975  
 Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn  
 980 985 990  
 Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp  
 995 1000 1005  
 Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys  
 1010 1015 1020  
 Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp  
 1025 1030 1035  
 Asn Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr  
 1040 1045 1050  
 Asn Gln Ala Thr Arg Pro Pro Gly Gly Cys His Ser Asp Glu Phe  
 1055 1060 1065  
 Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys  
 1070 1075 1080  
 Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys  
 1085 1090 1095  
 Glu Gly Val Thr His Val Cys Asp Pro Asn Val Lys Phe Gly Cys  
 1100 1105 1110  
 Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly  
 1115 1120 1125

Nonprovisional IP-017.ST25.txt

Asp Ser Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ala  
 1130 1135 1140  
 Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser  
 1145 1150 1155  
 Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Lys Asp Asp Cys  
 1160 1165 1170  
 Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu  
 1175 1180 1185  
 Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu  
 1190 1195 1200  
 Gly Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Ser Asp  
 1205 1210 1215  
 Asn His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys  
 1220 1225 1230  
 Cys Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser  
 1235 1240 1245  
 Cys Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg  
 1250 1255 1260  
 Ser Leu Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His  
 1265 1270 1275  
 Glu Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu  
 1280 1285 1290  
 Val Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser  
 1295 1300 1305  
 Gln Ser Ala Leu Tyr Trp Thr Asp Val Val Glu Asp Lys Ile Tyr  
 1310 1315 1320  
 Arg Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val  
 1325 1330 1335  
 Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp  
 1340 1345 1350  
 Trp Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln  
 1355 1360 1365  
 Ile Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu  
 1370 1375 1380

Nonprovisional IP-017.ST25.txt

Ala Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg  
 1385 1390 1395  
 Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg  
 1400 1405 1410  
 Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr Ile His  
 1415 1420 1425  
 Arg Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp  
 1430 1435 1440  
 Tyr Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala  
 1445 1450 1455  
 Ile Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu  
 1460 1465 1470  
 Arg Gly His Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr  
 1475 1480 1485  
 Gly Gly Glu Val Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala  
 1490 1495 1500  
 Lys Ala Asn Lys Trp Thr Gly His Asn Val Thr Val Val Gln Arg  
 1505 1510 1515  
 Thr Asn Thr Gln Pro Phe Asp Leu Gln Val Tyr His Pro Ser Arg  
 1520 1525 1530  
 Gln Pro Met Ala Pro Asn Pro Cys Glu Ala Asn Gly Gly Arg Gly  
 1535 1540 1545  
 Pro Cys Ser His Leu Cys Leu Ile Asn Tyr Asn Arg Thr Val Ser  
 1550 1555 1560  
 Cys Ala Cys Pro His Leu Met Lys Leu His Lys Asp Asn Thr Thr  
 1565 1570 1575  
 Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr Ala Arg Gln Met Glu  
 1580 1585 1590  
 Ile Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr Asn Tyr Ile Ile  
 1595 1600 1605  
 Ser Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val Leu Asp Tyr  
 1610 1615 1620  
 Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg Thr Gln  
 1625 1630 1635

Nonprovisional IP-017.ST25.txt

Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr Val  
 1640 1645 1650

Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp  
 1655 1660 1665

Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys  
 1670 1675 1680

Gln Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val  
 1685 1690 1695

Val Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu  
 1700 1705 1710

Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala  
 1715 1720 1725

Asn Met Asp Gly Ser Asn His Thr Leu Leu Phe Ser Gly Gln Lys  
 1730 1735 1740

Gly Pro Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr  
 1745 1750 1755

Trp Ile Ser Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp  
 1760 1765 1770

Gly Ser Glu Leu Glu Val Ile Asp Thr Met Arg Ser Gln Leu Gly  
 1775 1780 1785

Lys Ala Thr Ala Leu Ala Ile Met Gly Asp Lys Leu Trp Trp Ala  
 1790 1795 1800

Asp Gln Val Ser Glu Lys Met Gly Thr Cys Asn Lys Ala Asp Gly  
 1805 1810 1815

Ser Gly Ser Val Val Leu Arg Asn Ser Thr Thr Leu Val Met His  
 1820 1825 1830

Met Lys Val Tyr Asp Glu Ser Ile Gln Leu Glu His Glu Gly Thr  
 1835 1840 1845

Asn Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln Leu Cys Leu  
 1850 1855 1860

Pro Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala Gly Tyr  
 1865 1870 1875

Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser Phe  
 1880 1885 1890



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Leu 1895 Leu Tyr Ser Val His Glu 1900 Gly Ile Arg Gly Ile 1905 Pro Leu Asp  
 Pro 1910 Asn Asp Lys Ser Asp Ala 1915 Leu Val Pro Val Ser 1920 Gly Thr Ser  
 Leu 1925 Ala Val Gly Ile Asp Phe 1930 His Ala Glu Asn Asp 1935 Thr Ile Tyr  
 Trp 1940 Val Asp Met Gly Leu Ser 1945 Thr Ile Ser Arg Ala 1950 Lys Arg Asp  
 Gln 1955 Thr Trp Arg Glu Asp Val 1960 Val Thr Asn Gly Ile 1965 Gly Arg Val  
 Glu 1970 Gly Ile Ala Val Asp Trp 1975 Ile Ala Gly Asn Ile 1980 Tyr Trp Thr  
 Asp 1985 Gln Gly Phe Asp Val Ile 1990 Glu Val Ala Arg Leu 1995 Asn Gly Ser  
 Phe 2000 Arg Tyr Val Val Ile Ser 2005 Gln Gly Leu Asp Lys 2010 Pro Arg Ala  
 Ile 2015 Thr Val His Pro Glu Lys 2020 Gly Tyr Leu Phe Trp 2025 Thr Glu Trp  
 Gly 2030 His Tyr Pro Arg Ile Glu 2035 Arg Ser Arg Leu Asp 2040 Gly Thr Glu  
 Arg 2045 Val Val Leu Val Asn Val 2050 Ser Ile Ser Trp Pro 2055 Asn Gly Ile  
 Ser 2060 Val Asp Tyr Gln Gly Gly 2065 Lys Leu Tyr Trp Cys 2070 Asp Ala Arg  
 Met 2075 Asp Lys Ile Glu Arg Ile 2080 Asp Leu Glu Thr Gly 2085 Glu Asn Arg  
 Glu 2090 Val Val Leu Ser Ser Asn 2095 Asn Met Asp Met Phe 2100 Ser Val Ser  
 Val 2105 Phe Glu Asp Phe Ile Tyr 2110 Trp Ser Asp Arg Thr 2115 His Ala Asn  
 Gly 2120 Ser Ile Lys Arg Gly Cys 2125 Lys Asp Asn Ala Thr 2130 Asp Ser Val  
 Pro 2135 Leu Arg Thr Gly Ile Gly 2140 Val Gln Leu Lys Asp 2145 Ile Lys Val

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Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala Val Ala  
 2150 2155 2160  
 Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Gly Gly Gln  
 2165 2170 2175  
 Arg Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala  
 2180 2185 2190  
 Ser Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr  
 2195 2200 2205  
 Ile Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala  
 2210 2215 2220  
 Pro Val Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile  
 2225 2230 2235  
 Ala Leu Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro  
 2240 2245 2250  
 Asn Arg Ile Phe Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln  
 2255 2260 2265  
 Ile Asn Asp Asp Gly Ser Gly Arg Thr Thr Ile Val Glu Asn Val  
 2270 2275 2280  
 Gly Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu  
 2285 2290 2295  
 Tyr Trp Thr Ser Tyr Thr Thr Ser Thr Ile Thr Arg His Thr Val  
 2300 2305 2310  
 Asp Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr  
 2315 2320 2325  
 Met Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys  
 2330 2335 2340  
 Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Leu His Pro Ser  
 2345 2350 2355  
 Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile  
 2360 2365 2370  
 Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg  
 2375 2380 2385  
 Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu  
 2390 2395 2400

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Arg Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser  
 2405 2410 2415  
 Glu Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile  
 2420 2425 2430  
 Phe Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys  
 2435 2440 2445  
 Tyr Val Gly Ser Asp Met Lys Leu Leu Arg Val Asp Ile Pro Gln  
 2450 2455 2460  
 Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys  
 2465 2470 2475  
 Glu Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu  
 2480 2485 2490  
 Cys Leu Leu Thr His Gln Gly His Val Asn Cys Ser Cys Arg Gly  
 2495 2500 2505  
 Gly Arg Ile Leu Gln Glu Asp Phe Thr Cys Arg Ala Val Asn Ser  
 2510 2515 2520  
 Ser Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys  
 2525 2530 2535  
 Ile Ser Phe Ser Leu Thr Cys Asp Gly Val Ser His Cys Lys Asp  
 2540 2545 2550  
 Lys Ser Asp Glu Lys Pro Ser Tyr Cys Asn Ser Arg Arg Cys Lys  
 2555 2560 2565  
 Lys Thr Phe Arg Gln Cys Asn Asn Gly Arg Cys Val Ser Asn Met  
 2570 2575 2580  
 Leu Trp Cys Asn Gly Val Asp Asp Cys Gly Asp Gly Ser Asp Glu  
 2585 2590 2595  
 Ile Pro Cys Asn Lys Thr Ala Cys Gly Val Gly Glu Phe Arg Cys  
 2600 2605 2610  
 Arg Asp Gly Ser Cys Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe  
 2615 2620 2625  
 Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser Ala Thr  
 2630 2635 2640  
 Asp Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val Leu Phe  
 2645 2650 2655

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Gln Pro Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp Val  
 2660 2665 2670

Cys Asp Gly Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp  
 2675 2680 2685

Cys Pro Gly Val Lys Arg Pro Arg Cys Pro Leu Asn Tyr Phe Ala  
 2690 2695 2700

Cys Pro Ser Gly Arg Cys Ile Pro Met Ser Trp Thr Cys Asp Lys  
 2705 2710 2715

Glu Asp Asp Cys Glu Asn Gly Glu Asp Glu Thr His Cys Asn Lys  
 2720 2725 2730

Phe Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile  
 2735 2740 2745

Ser Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly  
 2750 2755 2760

Ser Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser  
 2765 2770 2775

Ser Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp  
 2780 2785 2790

Leu Cys Asp Gly Asp Lys Asp Cys Thr Asp Gly Ala Asp Glu Ser  
 2795 2800 2805

Val Thr Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu  
 2810 2815 2820

Phe Met Cys Gln Asn Arg Leu Cys Ile Pro Lys His Phe Val Cys  
 2825 2830 2835

Asp His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu  
 2840 2845 2850

Cys Glu Tyr Pro Thr Cys Gly Pro Asn Glu Phe Arg Cys Ala Asn  
 2855 2860 2865

Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn  
 2870 2875 2880

Asp Cys His Asp His Ser Asp Glu Ala Pro Lys Asn Pro His Cys  
 2885 2890 2895

Thr Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys  
 2900 2905 2910

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Ser	Ser	Gly	Arg	Cys	Val	Ala	Glu	Ala	Leu	Leu	Cys	Asn	Gly	Gln
	2915					2920					2925			
Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Arg	Gly	Cys	His	Val	Asn
	2930					2935					2940			
Glu	Cys	Leu	Ser	Arg	Lys	Leu	Ser	Gly	Cys	Ser	Gln	Asp	Cys	Glu
	2945					2950					2955			
Asp	Leu	Lys	Ile	Gly	Phe	Lys	Cys	Arg	Cys	Arg	Pro	Gly	Phe	Arg
	2960					2965					2970			
Leu	Lys	Asp	Asp	Gly	Arg	Thr	Cys	Ala	Asp	Leu	Asp	Glu	Cys	Ser
	2975					2980					2985			
Thr	Thr	Phe	Pro	Cys	Ser	Gln	Leu	Cys	Ile	Asn	Thr	His	Gly	Ser
	2990					2995					3000			
Tyr	Lys	Cys	Leu	Cys	Val	Glu	Gly	Tyr	Ala	Pro	Arg	Gly	Gly	Asp
	3005					3010					3015			
Pro	His	Ser	Cys	Lys	Ala	Val	Thr	Asp	Glu	Glu	Pro	Phe	Leu	Ile
	3020					3025					3030			
Phe	Ala	Asn	Arg	Tyr	Tyr	Leu	Arg	Lys	Leu	Asn	Leu	Asp	Gly	Ser
	3035					3040					3045			
Asn	Tyr	Thr	Leu	Leu	Lys	Gln	Gly	Leu	Asn	Asn	Ala	Val	Ala	Leu
	3050					3055					3060			
Asp	Phe	Asp	Tyr	Arg	Glu	Gln	Met	Ile	Tyr	Trp	Thr	Asp	Val	Thr
	3065					3070					3075			
Thr	Gln	Gly	Ser	Met	Ile	Arg	Arg	Met	His	Leu	Asn	Gly	Ser	Asn
	3080					3085					3090			
Val	Gln	Val	Leu	His	Arg	Thr	Gly	Leu	Ser	Asn	Pro	Asp	Gly	Leu
	3095					3100					3105			
Ala	Val	Asp	Trp	Val	Gly	Gly	Asn	Leu	Tyr	Trp	Cys	Asp	Lys	Gly
	3110					3115					3120			
Arg	Asp	Thr	Ile	Glu	Val	Ser	Lys	Leu	Asn	Gly	Ala	Tyr	Arg	Thr
	3125					3130					3135			
Val	Leu	Val	Ser	Ser	Gly	Leu	Arg	Glu	Pro	Arg	Ala	Leu	Val	Val
	3140					3145					3150			
Asp	Val	Gln	Asn	Gly	Tyr	Leu	Tyr	Trp	Thr	Asp	Trp	Gly	Asp	His
	3155					3160					3165			

Nonprovisional IP-017.ST25.txt

Ser Leu Ile Gly Arg Ile Gly Met Asp Gly Ser Gly Arg Ser Ile  
 3170 3175 3180  
 Ile Val Asp Thr Lys Ile Thr Trp Pro Asn Gly Leu Thr Val Asp  
 3185 3190 3195  
 Tyr Val Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr  
 3200 3205 3210  
 Ile Glu Phe Ala Ser Leu Asp Gly Ser Asn Arg His Val Val Leu  
 3215 3220 3225  
 Ser Gln Asp Ile Pro His Ile Phe Ala Leu Thr Leu Phe Glu Asp  
 3230 3235 3240  
 Tyr Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala  
 3245 3250 3255  
 His Lys Thr Thr Gly Ala Asn Lys Thr Leu Leu Ile Ser Thr Leu  
 3260 3265 3270  
 His Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro  
 3275 3280 3285  
 Asp Val Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser  
 3290 3295 3300  
 Asn Leu Cys Leu Leu Ser Pro Gly Gly Gly His Lys Cys Ala Cys  
 3305 3310 3315  
 Pro Thr Asn Phe Tyr Leu Gly Gly Asp Gly Arg Thr Cys Val Ser  
 3320 3325 3330  
 Asn Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile  
 3335 3340 3345  
 Pro Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His  
 3350 3355 3360  
 Ser Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro Gly  
 3365 3370 3375  
 Gln Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe Ile  
 3380 3385 3390  
 Cys Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn  
 3395 3400 3405  
 Cys Asp Ile His Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn  
 3410 3415 3420

Nonprovisional IP-017.ST25.txt

Thr	Asn	Arg	Cys	Ile	Pro	Gly	Ile	Phe	Arg	Cys	Asn	Gly	Gln	Asp
	3425					3430					3435			
Asn	Cys	Gly	Asp	Gly	Glu	Asp	Glu	Arg	Asp	Cys	Pro	Glu	Val	Thr
	3440					3445					3450			
Cys	Ala	Pro	Asn	Gln	Phe	Gln	Cys	Ser	Ile	Thr	Lys	Arg	Cys	Ile
	3455					3460					3465			
Pro	Arg	Val	Trp	Val	Cys	Asp	Arg	Asp	Asn	Asp	Cys	Val	Asp	Gly
	3470					3475					3480			
Ser	Asp	Glu	Pro	Ala	Asn	Cys	Thr	Gln	Met	Thr	Cys	Gly	Val	Asp
	3485					3490					3495			
Glu	Phe	Arg	Cys	Lys	Asp	Ser	Gly	Arg	Cys	Ile	Pro	Ala	Arg	Trp
	3500					3505					3510			
Lys	Cys	Asp	Gly	Glu	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Pro
	3515					3520					3525			
Lys	Glu	Glu	Cys	Asp	Glu	Arg	Thr	Cys	Glu	Pro	Tyr	Gln	Phe	Arg
	3530					3535					3540			
Cys	Lys	Asn	Asn	Arg	Cys	Val	Pro	Gly	Arg	Trp	Gln	Cys	Asp	Tyr
	3545					3550					3555			
Asp	Asn	Asp	Cys	Gly	Asp	Asn	Ser	Asp	Glu	Glu	Ser	Cys	Thr	Pro
	3560					3565					3570			
Arg	Pro	Cys	Ser	Glu	Ser	Glu	Phe	Ser	Cys	Ala	Asn	Gly	Arg	Cys
	3575					3580					3585			
Ile	Ala	Gly	Arg	Trp	Lys	Cys	Asp	Gly	Asp	His	Asp	Cys	Ala	Asp
	3590					3595					3600			
Gly	Ser	Asp	Glu	Lys	Asp	Cys	Thr	Pro	Arg	Cys	Asp	Met	Asp	Gln
	3605					3610					3615			
Phe	Gln	Cys	Lys	Ser	Gly	His	Cys	Ile	Pro	Leu	Arg	Trp	Arg	Cys
	3620					3625					3630			
Asp	Ala	Asp	Ala	Asp	Cys	Met	Asp	Gly	Ser	Asp	Glu	Glu	Ala	Cys
	3635					3640					3645			
Gly	Thr	Gly	Val	Arg	Thr	Cys	Pro	Leu	Asp	Glu	Phe	Gln	Cys	Asn
	3650					3655					3660			
Asn	Thr	Leu	Cys	Lys	Pro	Leu	Ala	Trp	Lys	Cys	Asp	Gly	Glu	Asp
	3665					3670					3675			

## Nonprovisional IP-017.ST25.txt

Asp Cys Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg  
 3680 3685 3690  
 Phe Ile Cys Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg  
 3695 3700 3705  
 Val Cys Leu Trp Ile Gly Arg Gln Cys Asp Gly Val Asp Asn Cys  
 3710 3715 3720  
 Gly Asp Gly Thr Asp Glu Glu Asp Cys Glu Pro Pro Thr Ala Gln  
 3725 3730 3735  
 Asn Pro His Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln  
 3740 3745 3750  
 Arg Cys Leu Ser Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys  
 3755 3760 3765  
 Gly Asp Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp Pro Lys Leu  
 3770 3775 3780  
 Thr Ser Cys Ala Thr Asn Ala Ser Met Cys Gly Asp Glu Ala Arg  
 3785 3790 3795  
 Cys Val Arg Thr Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser Gly  
 3800 3805 3810  
 Phe His Thr Val Pro Gly Gln Pro Gly Cys Gln Asp Ile Asn Glu  
 3815 3820 3825  
 Cys Leu Arg Phe Gly Thr Cys Ser Gln Leu Cys Asn Asn Thr Lys  
 3830 3835 3840  
 Gly Gly His Leu Cys Ser Cys Ala Arg Asn Phe Met Lys Thr His  
 3845 3850 3855  
 Asn Thr Cys Lys Ala Glu Gly Ser Glu Tyr Gln Val Leu Tyr Ile  
 3860 3865 3870  
 Ala Asp Asp Asn Glu Ile Arg Ser Leu Phe Pro Gly His Pro His  
 3875 3880 3885  
 Ser Ala Tyr Glu Gln Thr Phe Gln Gly Asp Glu Ser Val Arg Ile  
 3890 3895 3900  
 Asp Ala Met Asp Val His Val Lys Ala Gly Arg Val Tyr Trp Thr  
 3905 3910 3915  
 Asn Trp His Thr Gly Thr Ile Ser Tyr Arg Ser Leu Pro Pro Ala  
 3920 3925 3930



## Nonprovisional IP-017.ST25.txt

Ala Pro Pro Thr Thr Ser Asn Arg His Arg Arg Gln Ile Asp Arg  
 3935 3940 3945  
 Gly Val Thr His Leu Asn Ile Ser Gly Leu Lys Met Pro Arg Gly  
 3950 3955 3960  
 Ile Ala Ile Asp Trp Val Ala Gly Asn Val Tyr Trp Thr Asp Ser  
 3965 3970 3975  
 Gly Arg Asp Val Ile Glu Val Ala Gln Met Lys Gly Glu Asn Arg  
 3980 3985 3990  
 Lys Thr Leu Ile Ser Gly Met Ile Asp Glu Pro His Ala Ile Val  
 3995 4000 4005  
 Val Asp Pro Leu Arg Gly Thr Met Tyr Trp Ser Asp Trp Gly Asn  
 4010 4015 4020  
 His Pro Lys Ile Glu Thr Ala Ala Met Asp Gly Thr Leu Arg Glu  
 4025 4030 4035  
 Thr Leu Val Gln Asp Asn Ile Gln Trp Pro Thr Gly Leu Ala Val  
 4040 4045 4050  
 Asp Tyr His Asn Glu Arg Leu Tyr Trp Ala Asp Ala Lys Leu Ser  
 4055 4060 4065  
 Val Ile Gly Ser Ile Arg Leu Asn Gly Thr Asp Pro Ile Val Ala  
 4070 4075 4080  
 Ala Asp Ser Lys Arg Gly Leu Ser His Pro Phe Ser Ile Asp Val  
 4085 4090 4095  
 Phe Glu Asp Tyr Ile Tyr Gly Val Thr Tyr Ile Asn Asn Arg Val  
 4100 4105 4110  
 Phe Lys Ile His Lys Phe Gly His Ser Pro Leu Ile Asn Leu Thr  
 4115 4120 4125  
 Gly Gly Leu Ser His Ala Ser Asp Val Val Leu Tyr His Gln His  
 4130 4135 4140  
 Lys Gln Pro Glu Val Thr Asn Pro Cys Asp Arg Lys Lys Cys Glu  
 4145 4150 4155  
 Trp Leu Cys Leu Leu Ser Pro Ser Gly Pro Val Cys Thr Cys Pro  
 4160 4165 4170  
 Asn Gly Lys Arg Leu Asp Asn Gly Thr Cys Val Pro Val Pro Ser  
 4175 4180 4185

## Nonprovisional IP-017.ST25.txt

Pro Thr Pro Pro Pro Asp Ala Pro Arg Pro Gly Thr Cys Thr Leu  
 4190 4195 4200  
 Gln Cys Phe Asn Gly Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln  
 4205 4210 4215  
 Pro Lys Cys Arg Cys Gln Pro Arg Tyr Thr Gly Asp Lys Cys Glu  
 4220 4225 4230  
 Leu Asp Gln Cys Trp Glu Tyr Cys His Asn Gly Gly Thr Cys Ala  
 4235 4240 4245  
 Ala Ser Pro Ser Gly Met Pro Thr Cys Arg Cys Pro Thr Gly Phe  
 4250 4255 4260  
 Thr Gly Pro Lys Cys Thr Ala Gln Val Cys Ala Gly Tyr Cys Ser  
 4265 4270 4275  
 Asn Asn Ser Thr Cys Thr Val Asn Gln Gly Asn Gln Pro Gln Cys  
 4280 4285 4290  
 Arg Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys Gln Tyr Arg Gln  
 4295 4300 4305  
 Cys Ser Gly Phe Cys Glu Asn Phe Gly Thr Cys Gln Met Ala Ala  
 4310 4315 4320  
 Asp Gly Ser Arg Gln Cys Arg Cys Thr Val Tyr Phe Glu Gly Pro  
 4325 4330 4335  
 Arg Cys Glu Val Asn Lys Cys Ser Arg Cys Leu Gln Gly Ala Cys  
 4340 4345 4350  
 Val Val Asn Lys Gln Thr Gly Asp Val Thr Cys Asn Cys Thr Asp  
 4355 4360 4365  
 Gly Arg Val Ala Pro Ser Cys Leu Thr Cys Ile Asp His Cys Ser  
 4370 4375 4380  
 Asn Gly Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys  
 4385 4390 4395  
 Gln Cys Pro Pro His Met Thr Gly Pro Arg Cys Glu Glu Gln Val  
 4400 4405 4410  
 Val Ser Gln Gln Gln Pro Gly His Met Ala Ser Ile Leu Ile Pro  
 4415 4420 4425  
 Leu Leu Leu Leu Leu Leu Leu Leu Val Ala Gly Val Val Phe  
 4430 4435 4440

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Trp Tyr Lys Arg Arg Val Arg Gly Ala Lys Gly Phe Gln His Gln  
 4445 4450 4455

Arg Met Thr Asn Gly Ala Met Asn Val Glu Ile Gly Asn Pro Thr  
 4460 4465 4470

Tyr Lys Met Tyr Glu Gly Gly Glu Pro Asp Asp Val Gly Gly Leu  
 4475 4480 4485

Leu Asp Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro Thr Asn Phe  
 4490 4495 4500

Thr Asn Pro Val Tyr Ala Thr Leu Tyr Met Gly Gly His Gly Ser  
 4505 4510 4515

Arg His Ser Leu Ala Ser Thr Asp Glu Lys Arg Glu Leu Leu Gly  
 4520 4525 4530

Arg Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala  
 4535 4540 4545

<210> 68  
 <211> 4544  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 68

Met Leu Thr Pro Pro Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu  
 1 5 10 15

Val Ala Ala Ala Ile Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln Phe  
 20 25 30

Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys Asp  
 35 40 45

Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile Cys  
 50 55 60

Pro Gln Ser Lys Ala Gln Arg Cys Gln Pro Asn Glu His Asn Cys Leu  
 65 70 75 80

Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Val Gln  
 85 90 95

Asp Cys Met Asp Gly Ser Asp Glu Gly Pro His Cys Arg Glu Leu Gln  
 100 105 110

Gly Asn Cys Ser Arg Leu Gly Cys Gln His His Cys Val Pro Thr Leu  
 115 120 125

Asp Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala Asp  
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130

135

140

Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr Cys  
 145 150 155 160

Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Ile Cys Gly Cys Val  
 165 170 175

Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys Asn  
 180 185 190

Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln Asn  
 195 200 205

Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr Pro  
 210 215 220

Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn Glu  
 225 230 235 240

Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln Leu  
 245 250 255

Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His Thr  
 260 265 270

Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile Asp  
 275 280 285

Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg Ile  
 290 295 300

Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp Leu  
 305 310 315 320

Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly Lys  
 325 330 335

Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys Asp  
 340 345 350

Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val Phe  
 355 360 365

Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp Ala  
 370 375 380

Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys Gly  
 385 390 395 400

Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly Leu  
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405

410

415

Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala Asn  
 420 425 430  
 Ala Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser Thr  
 435 440 445  
 Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His Ile  
 450 455 460  
 Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu Asn  
 465 470 475 480  
 Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu Ala  
 485 490 495  
 Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser Leu  
 500 505 510  
 Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe Leu  
 515 520 525  
 Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met Gly  
 530 535 540  
 Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met Asn  
 545 550 555 560  
 Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe Ala  
 565 570 575  
 Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu  
 580 585 590  
 Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val Ala  
 595 600 605  
 Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro Lys  
 610 615 620  
 Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg Lys  
 625 630 635 640  
 Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val Asp  
 645 650 655  
 Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro Lys  
 660 665 670  
 Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser His  
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675

680

685

Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly Leu  
 690 695 700  
 Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe Tyr  
 705 710 715 720  
 Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile Val  
 725 730 735  
 Tyr Glu Gly pro Glu Leu Asn His Ala Phe Gly Leu Cys His His Gly  
 740 745 750  
 Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg Leu  
 755 760 765  
 Glu Arg Gly Val Gly Gly Ala Pro Pro Thr Val Thr Leu Leu Arg Ser  
 770 775 780  
 Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln Gln  
 785 790 795 800  
 Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser Ser  
 805 810 815  
 Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu Asp  
 820 825 830  
 Gln Val Leu Asp Ala Asp Gly Val Thr Cys Leu Ala Asn Pro Ser Tyr  
 835 840 845  
 Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser  
 850 855 860  
 Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu  
 865 870 875 880  
 Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro  
 885 890 895  
 Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp  
 900 905 910  
 Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn  
 915 920 925  
 Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala  
 930 935 940  
 Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp  
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945 Nonprovisional IP-017.ST25.txt 955 960  
 Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys  
 965 970 975  
 Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile  
 980 985 990  
 Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu  
 995 1000 1005  
 Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn  
 1010 1015 1020  
 Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn  
 1025 1030 1035  
 Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn  
 1040 1045 1050  
 Gln Ala Thr Arg Pro Pro Gly Gly Cys His Thr Asp Glu Phe Gln  
 1055 1060 1065  
 Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp  
 1070 1075 1080  
 Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu  
 1085 1090 1095  
 Gly Val Thr His Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys  
 1100 1105 1110  
 Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly Asp  
 1115 1120 1125  
 Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ser Leu  
 1130 1135 1140  
 Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val  
 1145 1150 1155  
 Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly  
 1160 1165 1170  
 Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu Asn  
 1175 1180 1185  
 Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu Gly  
 1190 1195 1200  
 Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Pro Asp Asn  
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1205 1210 1215  
 His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys Cys  
 1220 1225 1230  
 Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser Cys  
 1235 1240 1245  
 Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg Ser  
 1250 1255 1260  
 Leu Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His Glu  
 1265 1270 1275  
 Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu Val  
 1280 1285 1290  
 Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser Gln  
 1295 1300 1305  
 Ser Ala Leu Tyr Trp Thr Asp Val Val Glu Asp Lys Ile Tyr Arg  
 1310 1315 1320  
 Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val Val  
 1325 1330 1335  
 Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp Trp  
 1340 1345 1350  
 Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln Ile  
 1355 1360 1365  
 Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu Ala  
 1370 1375 1380  
 Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg Asp  
 1385 1390 1395  
 Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg Ile  
 1400 1405 1410  
 Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr Val His Arg  
 1415 1420 1425  
 Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp Tyr  
 1430 1435 1440  
 Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala Ile  
 1445 1450 1455  
 Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu Arg  
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1460													
Gly	His	Glu	Phe	Leu	Ser	His	Pro	Phe	Ala	Val	Thr	Leu	Tyr
1475						1480					1485		
Gly	Glu	Val	Tyr	Trp	Thr	Asp	Trp	Arg	Thr	Asn	Thr	Leu	Ala
1490						1495					1500		
Ala	Asn	Lys	Trp	Thr	Gly	His	Asn	Val	Thr	Val	Val	Gln	Arg
1505						1510					1515		
Asn	Thr	Gln	Pro	Phe	Asp	Leu	Gln	Val	Tyr	His	Pro	Ser	Arg
1520						1525					1530		
Pro	Met	Ala	Pro	Asn	Pro	Cys	Glu	Ala	Asn	Gly	Gly	Gln	Gly
1535						1540					1545		
Cys	Ser	His	Leu	Cys	Leu	Ile	Asn	Tyr	Asn	Arg	Thr	Val	Ser
1550						1555					1560		
Ala	Cys	Pro	His	Leu	Met	Lys	Leu	His	Lys	Asp	Asn	Thr	Thr
1565						1570					1575		
Tyr	Glu	Phe	Lys	Lys	Phe	Leu	Leu	Tyr	Ala	Arg	Gln	Met	Glu
1580						1585					1590		
Arg	Gly	Val	Asp	Leu	Asp	Ala	Pro	Tyr	Tyr	Asn	Tyr	Ile	Ile
1595						1600					1605		
Phe	Thr	Val	Pro	Asp	Ile	Asp	Asn	Val	Thr	Val	Leu	Asp	Tyr
1610						1615					1620		
Ala	Arg	Glu	Gln	Arg	Val	Tyr	Trp	Ser	Asp	Val	Arg	Thr	Gln
1625						1630					1635		
Ile	Lys	Arg	Ala	Phe	Ile	Asn	Gly	Thr	Gly	Val	Glu	Thr	Val
1640						1645					1650		
Ser	Ala	Asp	Leu	Pro	Asn	Ala	His	Gly	Leu	Ala	Val	Asp	Trp
1655						1660					1665		
Ser	Arg	Asn	Leu	Phe	Trp	Thr	Ser	Tyr	Asp	Thr	Asn	Lys	Lys
1670						1675					1680		
Ile	Asn	Val	Ala	Arg	Leu	Asp	Gly	Ser	Phe	Lys	Asn	Ala	Val
1685						1690					1695		
Gln	Gly	Leu	Glu	Gln	Pro	His	Gly	Leu	Val	Val	His	Pro	Leu
1700						1705					1710		
Gly	Lys	Leu	Tyr	Trp	Thr	Asp	Gly	Asp	Asn	Ile	Ser	Met	Ala

Nonprovisional IP-017.ST25.txt

1715														
						1720								1725
Met	Asp	Gly	Ser	Asn	Arg	Thr	Leu	Leu	Phe	Ser	Gly	Gln	Lys	Gly
	1730					1735					1740			
Pro	Val	Gly	Leu	Ala	Ile	Asp	Phe	Pro	Glu	Ser	Lys	Leu	Tyr	Trp
	1745					1750					1755			
Ile	Ser	Ser	Gly	Asn	His	Thr	Ile	Asn	Arg	Cys	Asn	Leu	Asp	Gly
	1760					1765					1770			
Ser	Gly	Leu	Glu	Val	Ile	Asp	Ala	Met	Arg	Ser	Gln	Leu	Gly	Lys
	1775					1780					1785			
Ala	Thr	Ala	Leu	Ala	Ile	Met	Gly	Asp	Lys	Leu	Trp	Trp	Ala	Asp
	1790					1795					1800			
Gln	Val	Ser	Glu	Lys	Met	Gly	Thr	Cys	Ser	Lys	Ala	Asp	Gly	Ser
	1805					1810					1815			
Gly	Ser	Val	Val	Leu	Arg	Asn	Ser	Thr	Thr	Leu	Val	Met	His	Met
	1820					1825					1830			
Lys	Val	Tyr	Asp	Glu	Ser	Ile	Gln	Leu	Asp	His	Lys	Gly	Thr	Asn
	1835					1840					1845			
Pro	Cys	Ser	Val	Asn	Asn	Gly	Asp	Cys	Ser	Gln	Leu	Cys	Leu	Pro
	1850					1855					1860			
Thr	Ser	Glu	Thr	Thr	Arg	Ser	Cys	Met	Cys	Thr	Ala	Gly	Tyr	Ser
	1865					1870					1875			
Leu	Arg	Ser	Gly	Gln	Gln	Ala	Cys	Glu	Gly	Val	Gly	Ser	Phe	Leu
	1880					1885					1890			
Leu	Tyr	Ser	Val	His	Glu	Gly	Ile	Arg	Gly	Ile	Pro	Leu	Asp	Pro
	1895					1900					1905			
Asn	Asp	Lys	Ser	Asp	Ala	Leu	Val	Pro	Val	Ser	Gly	Thr	Ser	Leu
	1910					1915					1920			
Ala	Val	Gly	Ile	Asp	Phe	His	Ala	Glu	Asn	Asp	Thr	Ile	Tyr	Trp
	1925					1930					1935			
Val	Asp	Met	Gly	Leu	Ser	Thr	Ile	Ser	Arg	Ala	Lys	Arg	Asp	Gln
	1940					1945					1950			
Thr	Trp	Arg	Glu	Asp	Val	Val	Thr	Asn	Gly	Ile	Gly	Arg	Val	Glu
	1955					1960					1965			
Gly	Ile	Ala	Val	Asp	Trp	Ile	Ala	Gly	Asn	Ile	Tyr	Trp	Thr	Asp

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1970														
Gln	Gly	Phe	Asp	Val	Ile	Glu	Val	Ala	Arg	Leu	Asn	Gly	Ser	Phe
	1985					1990					1995			
Arg	Tyr	Val	Val	Ile	Ser	Gln	Gly	Leu	Asp	Lys	Pro	Arg	Ala	Ile
	2000					2005					2010			
Thr	Val	His	Pro	Glu	Lys	Gly	Tyr	Leu	Phe	Trp	Thr	Glu	Trp	Gly
	2015					2020					2025			
Gln	Tyr	Pro	Arg	Ile	Glu	Arg	Ser	Arg	Leu	Asp	Gly	Thr	Glu	Arg
	2030					2035					2040			
Val	Val	Leu	Val	Asn	Val	Ser	Ile	Ser	Trp	Pro	Asn	Gly	Ile	Ser
	2045					2050					2055			
Val	Asp	Tyr	Gln	Asp	Gly	Lys	Leu	Tyr	Trp	Cys	Asp	Ala	Arg	Thr
	2060					2065					2070			
Asp	Lys	Ile	Glu	Arg	Ile	Asp	Leu	Glu	Thr	Gly	Glu	Asn	Arg	Glu
	2075					2080					2085			
Val	Val	Leu	Ser	Ser	Asn	Asn	Met	Asp	Met	Phe	Ser	Val	Ser	Val
	2090					2095					2100			
Phe	Glu	Asp	Phe	Ile	Tyr	Trp	Ser	Asp	Arg	Thr	His	Ala	Asn	Gly
	2105					2110					2115			
Ser	Ile	Lys	Arg	Gly	Ser	Lys	Asp	Asn	Ala	Thr	Asp	Ser	Val	Pro
	2120					2125					2130			
Leu	Arg	Thr	Gly	Ile	Gly	Val	Gln	Leu	Lys	Asp	Ile	Lys	Val	Phe
	2135					2140					2145			
Asn	Arg	Asp	Arg	Gln	Lys	Gly	Thr	Asn	Val	Cys	Ala	Val	Ala	Asn
	2150					2155					2160			
Gly	Gly	Cys	Gln	Gln	Leu	Cys	Leu	Tyr	Arg	Gly	Arg	Gly	Gln	Arg
	2165					2170					2175			
Ala	Cys	Ala	Cys	Ala	His	Gly	Met	Leu	Ala	Glu	Asp	Gly	Ala	Ser
	2180					2185					2190			
Cys	Arg	Glu	Tyr	Ala	Gly	Tyr	Leu	Leu	Tyr	Ser	Glu	Arg	Thr	Ile
	2195					2200					2205			
Leu	Lys	Ser	Ile	His	Leu	Ser	Asp	Glu	Arg	Asn	Leu	Asn	Ala	Pro
	2210					2215					2220			
Val	Gln	Pro	Phe	Glu	Asp	Pro	Glu	His	Met	Lys	Asn	Val	Ile	Ala

Nonprovisional IP-017.ST25.txt  
2230 2235

2225  
Leu Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro Asn  
2240 2245 2250  
Arg Ile Phe Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln Ile  
2255 2260 2265  
Asn Asp Asp Gly Ser Arg Arg Ile Thr Ile Val Glu Asn Val Gly  
2270 2275 2280  
Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu Tyr  
2285 2290 2295  
Trp Thr Ser Tyr Thr Thr Ser Thr Ile Thr Arg His Thr Val Asp  
2300 2305 2310  
Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr Met  
2315 2320 2325  
Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys Gln  
2330 2335 2340  
Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His Pro Ser Ile  
2345 2350 2355  
Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile Glu  
2360 2365 2370  
Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg Ala  
2375 2380 2385  
Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu Arg  
2390 2395 2400  
Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser Glu  
2405 2410 2415  
Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile Phe  
2420 2425 2430  
Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys His  
2435 2440 2445  
Val Gly Ser Asn Met Lys Leu Leu Arg Val Asp Ile Pro Gln Gln  
2450 2455 2460  
Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys Glu  
2465 2470 2475  
Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu Cys  
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Nonprovisional IP-017.ST25.txt														
2480					2485					2490				
Leu	Leu	Thr	His	Gln	Gly	His	Val	Asn	Cys	Ser	Cys	Arg	Gly	Gly
	2495					2500					2505			
Arg	Ile	Leu	Gln	Asp	Asp	Leu	Thr	Cys	Arg	Ala	Val	Asn	Ser	Ser
	2510					2515					2520			
Cys	Arg	Ala	Gln	Asp	Glu	Phe	Glu	Cys	Ala	Asn	Gly	Glu	Cys	Ile
	2525					2530					2535			
Asn	Phe	Ser	Leu	Thr	Cys	Asp	Gly	Val	Pro	His	Cys	Lys	Asp	Lys
	2540					2545					2550			
Ser	Asp	Glu	Lys	Pro	Ser	Tyr	Cys	Asn	Ser	Arg	Arg	Cys	Lys	Lys
	2555					2560					2565			
Thr	Phe	Arg	Gln	Cys	Ser	Asn	Gly	Arg	Cys	Val	Ser	Asn	Met	Leu
	2570					2575					2580			
Trp	Cys	Asn	Gly	Ala	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Ile
	2585					2590					2595			
Pro	Cys	Asn	Lys	Thr	Ala	Cys	Gly	Val	Gly	Glu	Phe	Arg	Cys	Arg
	2600					2605					2610			
Asp	Gly	Thr	Cys	Ile	Gly	Asn	Ser	Ser	Arg	Cys	Asn	Gln	Phe	Val
	2615					2620					2625			
Asp	Cys	Glu	Asp	Ala	Ser	Asp	Glu	Met	Asn	Cys	Ser	Ala	Thr	Asp
	2630					2635					2640			
Cys	Ser	Ser	Tyr	Phe	Arg	Leu	Gly	Val	Lys	Gly	Val	Leu	Phe	Gln
	2645					2650					2655			
Pro	Cys	Glu	Arg	Thr	Ser	Leu	Cys	Tyr	Ala	Pro	Ser	Trp	Val	Cys
	2660					2665					2670			
Asp	Gly	Ala	Asn	Asp	Cys	Gly	Asp	Tyr	Ser	Asp	Glu	Arg	Asp	Cys
	2675					2680					2685			
Pro	Gly	Val	Lys	Arg	Pro	Arg	Cys	Pro	Leu	Asn	Tyr	Phe	Ala	Cys
	2690					2695					2700			
Pro	Ser	Gly	Arg	Cys	Ile	Pro	Met	Ser	Trp	Thr	Cys	Asp	Lys	Glu
	2705					2710					2715			
Asp	Asp	Cys	Glu	His	Gly	Glu	Asp	Glu	Thr	His	Cys	Asn	Lys	Phe
	2720					2725					2730			
Cys	Ser	Glu	Ala	Gln	Phe	Glu	Cys	Gln	Asn	His	Arg	Cys	Ile	Ser

Nonprovisional IP-017.ST25.txt

2735 2740 2745

Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly Ser  
2750 2755 2760

Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser Ser  
2765 2770 2775

Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp Leu  
2780 2785 2790

Cys Asp Gly Asp Lys Asp Cys Ala Asp Gly Ala Asp Glu Ser Ile  
2795 2800 2805

Ala Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu Phe  
2810 2815 2820

Met Cys Gln Asn Arg Gln Cys Ile Pro Lys His Phe Val Cys Asp  
2825 2830 2835

His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu Cys  
2840 2845 2850

Glu Tyr Pro Thr Cys Gly Pro Ser Glu Phe Arg Cys Ala Asn Gly  
2855 2860 2865

Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp  
2870 2875 2880

Cys His Asp Gln Ser Asp Glu Ala Pro Lys Asn Pro His Cys Thr  
2885 2890 2895

Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys Ser  
2900 2905 2910

Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln Asp  
2915 2920 2925

Asp Cys Gly Asp Ser Ser Asp Glu Arg Gly Cys His Ile Asn Glu  
2930 2935 2940

Cys Leu Ser Arg Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu Asp  
2945 2950 2955

Leu Lys Ile Gly Phe Lys Cys Arg Cys Arg Pro Gly Phe Arg Leu  
2960 2965 2970

Lys Asp Asp Gly Arg Thr Cys Ala Asp Val Asp Glu Cys Ser Thr  
2975 2980 2985

Thr Phe Pro Cys Ser Gln Arg Cys Ile Asn Thr His Gly Ser Tyr

Nonprovisional IP-017.ST25.txt														
2990				2995				3000						
Lys	Cys	Leu	Cys	Val	Glu	Gly	Tyr	Ala	Pro	Arg	Gly	Gly	Asp	Pro
	3005					3010					3015			
His	Ser	Cys	Lys	Ala	Val	Thr	Asp	Glu	Glu	Pro	Phe	Leu	Ile	Phe
	3020					3025					3030			
Ala	Asn	Arg	Tyr	Tyr	Leu	Arg	Lys	Leu	Asn	Leu	Asp	Gly	Ser	Asn
	3035					3040					3045			
Tyr	Thr	Leu	Leu	Lys	Gln	Gly	Leu	Asn	Asn	Ala	Val	Ala	Leu	Asp
	3050					3055					3060			
Phe	Asp	Tyr	Arg	Glu	Gln	Met	Ile	Tyr	Trp	Thr	Asp	Val	Thr	Thr
	3065					3070					3075			
Gln	Gly	Ser	Met	Ile	Arg	Arg	Met	His	Leu	Asn	Gly	Ser	Asn	Val
	3080					3085					3090			
Gln	Val	Leu	His	Arg	Thr	Gly	Leu	Ser	Asn	Pro	Asp	Gly	Leu	Ala
	3095					3100					3105			
Val	Asp	Trp	Val	Gly	Gly	Asn	Leu	Tyr	Trp	Cys	Asp	Lys	Gly	Arg
	3110					3115					3120			
Asp	Thr	Ile	Glu	Val	Ser	Lys	Leu	Asn	Gly	Ala	Tyr	Arg	Thr	Val
	3125					3130					3135			
Leu	Val	Ser	Ser	Gly	Leu	Arg	Glu	Pro	Arg	Ala	Leu	Val	Val	Asp
	3140					3145					3150			
Val	Gln	Asn	Gly	Tyr	Leu	Tyr	Trp	Thr	Asp	Trp	Gly	Asp	His	Ser
	3155					3160					3165			
Leu	Ile	Gly	Arg	Ile	Gly	Met	Asp	Gly	Ser	Ser	Arg	Ser	Val	Ile
	3170					3175					3180			
Val	Asp	Thr	Lys	Ile	Thr	Trp	Pro	Asn	Gly	Leu	Thr	Leu	Asp	Tyr
	3185					3190					3195			
Val	Thr	Glu	Arg	Ile	Tyr	Trp	Ala	Asp	Ala	Arg	Glu	Asp	Tyr	Ile
	3200					3205					3210			
Glu	Phe	Ala	Ser	Leu	Asp	Gly	Ser	Asn	Arg	His	Val	Val	Leu	Ser
	3215					3220					3225			
Gln	Asp	Ile	Pro	His	Ile	Phe	Ala	Leu	Thr	Leu	Phe	Glu	Asp	Tyr
	3230					3235					3240			
Val	Tyr	Trp	Thr	Asp	Trp	Glu	Thr	Lys	Ser	Ile	Asn	Arg	Ala	His

Nonprovisional IP-017.ST25.txt

3245 3250 3255

Lys Thr Thr Gly Thr Asn Lys Thr Leu Leu Ile Ser Thr Leu His  
3260 3265 3270

Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro Asp  
3275 3280 3285

Val Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser Asn  
3290 3295 3300

Leu Cys Leu Leu Ser Pro Gly Gly Gly His Lys Cys Ala Cys Pro  
3305 3310 3315

Thr Asn Phe Tyr Leu Gly Ser Asp Gly Arg Thr Cys Val Ser Asn  
3320 3325 3330

Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile Pro  
3335 3340 3345

Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His Ser  
3350 3355 3360

Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro Gly Gln  
3365 3370 3375

Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe Ile Cys  
3380 3385 3390

Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn Cys  
3395 3400 3405

Asp Ile His Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr  
3410 3415 3420

Asn Arg Cys Ile Pro Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn  
3425 3430 3435

Cys Gly Asp Gly Glu Asp Glu Arg Asp Cys Pro Glu Val Thr Cys  
3440 3445 3450

Ala Pro Asn Gln Phe Gln Cys Ser Ile Thr Lys Arg Cys Ile Pro  
3455 3460 3465

Arg Val Trp Val Cys Asp Arg Asp Asn Asp Cys Val Asp Gly Ser  
3470 3475 3480

Asp Glu Pro Ala Asn Cys Thr Gln Met Thr Cys Gly Val Asp Glu  
3485 3490 3495

Phe Arg Cys Lys Asp Ser Gly Arg Cys Ile Pro Ala Arg Trp Lys



Nonprovisional IP-017.ST25.txt  
 3505 3510

3500  
 Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp Glu Pro Lys  
 3515 3520 3525  
 Glu Glu Cys Asp Glu Arg Thr Cys Glu Pro Tyr Gln Phe Arg Cys  
 3530 3535 3540  
 Lys Asn Asn Arg Cys Val Pro Gly Arg Trp Gln Cys Asp Tyr Asp  
 3545 3550 3555  
 Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu Ser Cys Thr Pro Arg  
 3560 3565 3570  
 Pro Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn Gly Arg Cys Ile  
 3575 3580 3585  
 Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp Cys Ala Asp Gly  
 3590 3595 3600  
 Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met Asp Gln Phe  
 3605 3610 3615  
 Gln Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Arg Cys Asp  
 3620 3625 3630  
 Ala Asp Ala Asp Cys Met Asp Gly Ser Asp Glu Glu Ala Cys Gly  
 3635 3640 3645  
 Thr Gly Val Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn  
 3650 3655 3660  
 Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp Asp  
 3665 3670 3675  
 Cys Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg Phe  
 3680 3685 3690  
 Val Cys Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg Val  
 3695 3700 3705  
 Cys Leu Trp Ile Gly Arg Gln Cys Asp Gly Thr Asp Asn Cys Gly  
 3710 3715 3720  
 Asp Gly Thr Asp Glu Glu Asp Cys Glu Pro Pro Thr Ala His Thr  
 3725 3730 3735  
 Thr His Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln Arg  
 3740 3745 3750  
 Cys Leu Ser Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys Gly  
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3755 3760 3765

Asp Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp Pro Lys Leu Thr  
3770 3775 3780

Ser Cys Ala Thr Asn Ala Ser Ile Cys Gly Asp Glu Ala Arg Cys  
3785 3790 3795

Val Arg Thr Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser Gly Phe  
3800 3805 3810

His Thr Val Pro Gly Gln Pro Gly Cys Gln Asp Ile Asn Glu Cys  
3815 3820 3825

Leu Arg Phe Gly Thr Cys Ser Gln Leu Cys Asn Asn Thr Lys Gly  
3830 3835 3840

Gly His Leu Cys Ser Cys Ala Arg Asn Phe Met Lys Thr His Asn  
3845 3850 3855

Thr Cys Lys Ala Glu Gly Ser Glu Tyr Gln Val Leu Tyr Ile Ala  
3860 3865 3870

Asp Asp Asn Glu Ile Arg Ser Leu Phe Pro Gly His Pro His Ser  
3875 3880 3885

Ala Tyr Glu Gln Ala Phe Gln Gly Asp Glu Ser Val Arg Ile Asp  
3890 3895 3900

Ala Met Asp Val His Val Lys Ala Gly Arg Val Tyr Trp Thr Asn  
3905 3910 3915

Trp His Thr Gly Thr Ile Ser Tyr Arg Ser Leu Pro Pro Ala Ala  
3920 3925 3930

Pro Pro Thr Thr Ser Asn Arg His Arg Arg Gln Ile Asp Arg Gly  
3935 3940 3945

Val Thr His Leu Asn Ile Ser Gly Leu Lys Met Pro Arg Gly Ile  
3950 3955 3960

Ala Ile Asp Trp Val Ala Gly Asn Val Tyr Trp Thr Asp Ser Gly  
3965 3970 3975

Arg Asp Val Ile Glu Val Ala Gln Met Lys Gly Glu Asn Arg Lys  
3980 3985 3990

Thr Leu Ile Ser Gly Met Ile Asp Glu Pro His Ala Ile Val Val  
3995 4000 4005

Asp Pro Leu Arg Gly Thr Met Tyr Trp Ser Asp Trp Gly Asn His

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4010						4015						4020			
Pro	Lys	Ile	Glu	Thr	Ala	Ala	Met	Asp	Gly	Thr	Leu	Arg	Glu	Thr	
	4025					4030					4035				
Leu	Val	Gln	Asp	Asn	Ile	Gln	Trp	Pro	Thr	Gly	Leu	Ala	Val	Asp	
	4040					4045					4050				
Tyr	His	Asn	Glu	Arg	Leu	Tyr	Trp	Ala	Asp	Ala	Lys	Leu	Ser	Val	
	4055					4060					4065				
Ile	Gly	Ser	Ile	Arg	Leu	Asn	Gly	Thr	Asp	Pro	Ile	Val	Ala	Ala	
	4070					4075					4080				
Asp	Ser	Lys	Arg	Gly	Leu	Ser	His	Pro	Phe	Ser	Ile	Asp	Val	Phe	
	4085					4090					4095				
Glu	Asp	Tyr	Ile	Tyr	Gly	Val	Thr	Tyr	Ile	Asn	Asn	Arg	Val	Phe	
	4100					4105					4110				
Lys	Ile	His	Lys	Phe	Gly	His	Ser	Pro	Leu	Val	Asn	Leu	Thr	Gly	
	4115					4120					4125				
Gly	Leu	Ser	His	Ala	Ser	Asp	Val	Val	Leu	Tyr	His	Gln	His	Lys	
	4130					4135					4140				
Gln	Pro	Glu	Val	Thr	Asn	Pro	Cys	Asp	Arg	Lys	Lys	Cys	Glu	Trp	
	4145					4150					4155				
Leu	Cys	Leu	Leu	Ser	Pro	Ser	Gly	Pro	Val	Cys	Thr	Cys	Pro	Asn	
	4160					4165					4170				
Gly	Lys	Arg	Leu	Asp	Asn	Gly	Thr	Cys	Val	Pro	Val	Pro	Ser	Pro	
	4175					4180					4185				
Thr	Pro	Pro	Pro	Asp	Ala	Pro	Arg	Pro	Gly	Thr	Cys	Asn	Leu	Gln	
	4190					4195					4200				
Cys	Phe	Asn	Gly	Gly	Ser	Cys	Phe	Leu	Asn	Ala	Arg	Arg	Gln	Pro	
	4205					4210					4215				
Lys	Cys	Arg	Cys	Gln	Pro	Arg	Tyr	Thr	Gly	Asp	Lys	Cys	Glu	Leu	
	4220					4225					4230				
Asp	Gln	Cys	Trp	Glu	His	Cys	Arg	Asn	Gly	Gly	Thr	Cys	Ala	Ala	
	4235					4240					4245				
Ser	Pro	Ser	Gly	Met	Pro	Thr	Cys	Arg	Cys	Pro	Thr	Gly	Phe	Thr	
	4250					4255					4260				
Gly	Pro	Lys	Cys	Thr	Gln	Gln	Val	Cys	Ala	Gly	Tyr	Cys	Ala	Asn	

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4265	Asn	Ser	Thr	Cys	Thr	Val	Asn	Gln	Gly	Asn	Gln	Pro	Gln	Cys	Arg
	4280						4285					4290			
	Cys	Leu	Pro	Gly	Phe	Leu	Gly	Asp	Arg	Cys	Gln	Tyr	Arg	Gln	Cys
	4295						4300					4305			
	Ser	Gly	Tyr	Cys	Glu	Asn	Phe	Gly	Thr	Cys	Gln	Met	Ala	Ala	Asp
	4310						4315					4320			
	Gly	Ser	Arg	Gln	Cys	Arg	Cys	Thr	Ala	Tyr	Phe	Glu	Gly	Ser	Arg
	4325						4330					4335			
	Cys	Glu	Val	Asn	Lys	Cys	Ser	Arg	Cys	Leu	Glu	Gly	Ala	Cys	Val
	4340						4345					4350			
	Val	Asn	Lys	Gln	Ser	Gly	Asp	Val	Thr	Cys	Asn	Cys	Thr	Asp	Gly
	4355						4360					4365			
	Arg	Val	Ala	Pro	Ser	Cys	Leu	Thr	Cys	Val	Gly	His	Cys	Ser	Asn
	4370						4375					4380			
	Gly	Gly	Ser	Cys	Thr	Met	Asn	Ser	Lys	Met	Met	Pro	Glu	Cys	Gln
	4385						4390					4395			
	Cys	Pro	Pro	His	Met	Thr	Gly	Pro	Arg	Cys	Glu	Glu	His	Val	Phe
	4400						4405					4410			
	Ser	Gln	Gln	Gln	Pro	Gly	His	Ile	Ala	Ser	Ile	Leu	Ile	Pro	Leu
	4415						4420					4425			
	Leu	Leu	Leu	Leu	Leu	Leu	Val	Leu	Val	Ala	Gly	Val	Val	Phe	Trp
	4430						4435					4440			
	Tyr	Lys	Arg	Arg	Val	Gln	Gly	Ala	Lys	Gly	Phe	Gln	His	Gln	Arg
	4445						4450					4455			
	Met	Thr	Asn	Gly	Ala	Met	Asn	Val	Glu	Ile	Gly	Asn	Pro	Thr	Tyr
	4460						4465					4470			
	Lys	Met	Tyr	Glu	Gly	Gly	Glu	Pro	Asp	Asp	Val	Gly	Gly	Leu	Leu
	4475						4480					4485			
	Asp	Ala	Asp	Phe	Ala	Leu	Asp	Pro	Asp	Lys	Pro	Thr	Asn	Phe	Thr
	4490						4495					4500			
	Asn	Pro	Val	Tyr	Ala	Thr	Leu	Tyr	Met	Gly	Gly	His	Gly	Ser	Arg
	4505						4510					4515			
	His	Ser	Leu	Ala	Ser	Thr	Asp	Glu	Lys	Arg	Glu	Leu	Leu	Gly	Arg

4520

Nonprovisional IP-017.ST25.txt  
4525 4530Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala  
4535 4540<210> 69  
<211> 4599  
<212> PRT  
<213> MOUSE

&lt;400&gt; 69

Met Ser Gln Leu Leu Leu Ala Ile Leu Thr Leu Ser Gly Leu Leu Pro  
1 5 10 15Asn Ala Glu Val Leu Ile Val Gly Ala Asn Gln Asp Gln His Leu Cys  
20 25 30Asp Pro Gly Glu Phe Leu Cys His Asp His Val Thr Cys Val Ser Gln  
35 40 45Ser Trp Leu Cys Asp Gly Asp Pro Asp Cys Pro Asp Gln Ser Asp Glu  
50 55 60Ser Leu Asp Thr Cys Pro Glu Glu Val Glu Ile Lys Cys Pro Leu Asn  
65 70 75 80His Ile Ala Cys His Gly Ser Ser Ala Cys Val His Leu Ser Lys Leu  
85 90 95Cys Asn Gly Val Val Asp Cys Pro Asp Gly Phe Asp Glu Gly Gly His  
100 105 110Cys Gln Glu Leu Leu Pro Ser Cys Gln Gln Leu Asn Cys Gln Phe Lys  
115 120 125Cys Ala Met Val Arg Asn Ala Thr Arg Cys Tyr Cys Glu Asp Gly Phe  
130 135 140Glu Val Ala Glu Asp Gly Arg Ser Cys Lys Asp Gln Asp Glu Cys Ser  
145 150 155 160Ile Tyr Gly Ile Cys Ser Gln Thr Cys Lys Asn Thr Tyr Gly Ser Tyr  
165 170 175Ala Cys Ser Cys Val Glu Gly Tyr Ile Met Gln Ser Asp Asn Arg Ser  
180 185 190Cys Lys Val Lys His Glu Pro Thr Asp Lys Ala Pro Met Leu Leu Ile  
195 200 205Ser Ser Leu Glu Thr Ile Glu Leu Phe Tyr Ile Asn Gly Ser Lys Met  
210 215 220

## Nonprovisional IP-017.ST25.txt

Thr Thr Leu Ser Ser Ala Asn Arg Asn Glu Ile His Thr Leu Asp Phe  
 225 230 235 240  
 Ile Tyr Ser Glu Glu Met Ile Cys Trp Ile Glu Ser Arg Glu Ser Ser  
 245 250 255  
 Asn Gln Leu Lys Cys Gly Gln Ile Thr Lys Ala Gly Arg Leu Thr Asp  
 260 265 270  
 Gln Arg Ile Ile Asn Ser Leu Gln Ser Phe Gln Asn Val Glu Gln Met  
 275 280 285  
 Ala Phe Asp Trp Leu Thr Arg Asn Ile Tyr Phe Val Asp His Val Ser  
 290 295 300  
 Asp Arg Ile Phe Val Cys Asn Phe Asn Gly Ser Val Cys Val Thr Leu  
 305 310 315 320  
 Ile Glu Ser Glu Leu His Asn Pro Lys Ala Ile Ala Ala Asp Pro Ile  
 325 330 335  
 Ala Gly Lys Leu Phe Phe Thr Asp Tyr Gly Asn Val Pro Lys Ile Glu  
 340 345 350  
 Arg Cys Asp Leu Asp Gly Met Asn Arg Thr Arg Ile Val Tyr Ser Lys  
 355 360 365  
 Ala Glu Gln Pro Ser Ala Leu Ala Leu Asp Leu Val Asn Arg Leu Val  
 370 375 380  
 Tyr Trp Val Asp Leu Tyr Leu Asp Tyr Val Gly Val Val Asp Tyr Gln  
 385 390 395 400  
 Gly Lys Asn Arg His Thr Ile Val Gln Gly Arg Gln Val Lys His Leu  
 405 410 415  
 Tyr Gly Ile Thr Val Phe Glu Asp Tyr Leu Tyr Ala Thr Ser Ser Asp  
 420 425 430  
 Asn Phe Asn Ile Ile Arg Ile Asn Arg Phe Asn Gly Thr Asp Ile His  
 435 440 445  
 Ser Ile Ile Lys Met Glu Ser Ala Arg Gly Ile Arg Thr Tyr Gln Lys  
 450 455 460  
 Arg Thr Gln Pro Thr Val Arg Ser His Ala Cys Glu Val Asp Ala Tyr  
 465 470 475 480  
 Gly Met Pro Gly Gly Cys Ser His Ile Cys Leu Leu Ser Ser Ser Tyr  
 485 490 495

## Nonprovisional IP-017.ST25.txt

Lys Thr Arg Thr Cys Arg Cys Arg Thr Gly Phe Asn Met Gly Ser Asp  
 500 505 510  
 Gly Arg Ser Cys Lys Arg Pro Lys Asn Glu Leu Phe Leu Phe Tyr Gly  
 515 520 525  
 Lys Gly Arg Pro Gly Ile Val Arg Gly Met Asp Leu Asn Thr Lys Ile  
 530 535 540  
 Ala Asp Glu Cys Met Ile Pro Ile Glu Asn Leu Val Asn Pro Arg Ala  
 545 550 555 560  
 Leu Asp Phe His Ala Glu Ala Asn Tyr Ile Tyr Phe Ala Asp Thr Thr  
 565 570 575  
 Ser Phe Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu Arg Glu Thr  
 580 585 590  
 Ile Leu Lys Asp Asp Leu Asp Asn Val Glu Gly Ile Ala Val Asp Trp  
 595 600 605  
 Ile Gly Asn Asn Leu Tyr Trp Thr Asn Asp Gly His Arg Lys Thr Ile  
 610 615 620  
 Asn Val Ala Arg Leu Glu Lys Ala Ser Gln Ser Arg Lys Thr Leu Leu  
 625 630 635 640  
 Glu Gly Gly Met Ser His Pro Arg Ala Ile Val Val Asp Pro Val Asn  
 645 650 655  
 Gly Trp Met Tyr Trp Thr Asp Trp Lys Glu Asp Lys Ile Asp Asp Ser  
 660 665 670  
 Val Gly Arg Ile Glu Lys Ala Trp Met Asp Gly Val Asn Arg Gln Val  
 675 680 685  
 Phe Val Thr Ser Lys Met Leu Trp Pro Asn Gly Leu Thr Leu Asp Phe  
 690 695 700  
 His Thr Ser Thr Leu Tyr Trp Cys Asp Ala Tyr Tyr Asp His Ile Glu  
 705 710 715 720  
 Lys Val Phe Leu Asn Gly Thr His Arg Lys Val Val Tyr Ser Gly Lys  
 725 730 735  
 Glu Leu Asn His Pro Phe Gly Leu Ser His His Gly Asn Tyr Val Phe  
 740 745 750  
 Trp Thr Asp Tyr Met Asn Gly Ser Ile Phe Gln Leu Asp Leu Met Thr  
 755 760 765

## Nonprovisional IP-017.ST25.txt

Asn Glu Val Thr Leu Leu Arg His Glu Arg Ala Pro Leu Phe Gly Leu  
 770 775 780  
 Gln Ile Tyr Asp Pro Arg Lys Gln Gln Gly Asp Asn Met Cys Arg Ile  
 785 790 795 800  
 Asn Asn Gly Gly Cys Gly Thr Leu Cys Leu Ala Ile Pro Ala Gly Arg  
 805 810 815  
 Val Cys Ala Cys Ala Asp Asn Gln Leu Leu Asp Glu Asn Gly Thr Thr  
 820 825 830  
 Cys Thr Phe Asn Pro Glu Glu Ile Arg Phe His Ile Cys Lys Pro Gly  
 835 840 845  
 Glu Phe Arg Cys Lys Asn Lys His Cys Ile Gln Ala Arg Trp Lys Cys  
 850 855 860  
 Asp Gly Asp Asp Asp Cys Leu Asp Gly Ser Asp Glu Asp Ser Val Thr  
 865 870 875 880  
 Cys Phe Asn His Ser Cys Pro Asp Asp Gln Phe Lys Cys Gln Asn Asn  
 885 890 895  
 Arg Cys Ile Pro Lys Arg Trp Leu Cys Asp Gly Ala Asn Asp Cys Gly  
 900 905 910  
 Ser Asn Glu Asp Glu Ser Asn Gln Thr Cys Thr Ala Arg Thr Cys Gln  
 915 920 925  
 Ala Asp Gln Phe Ser Cys Gly Asn Gly Arg Cys Ile Pro Thr Ala Trp  
 930 935 940  
 Leu Cys Asp Arg Glu Asp Asp Cys Gly Asp Gln Thr Asp Glu Val Ala  
 945 950 955 960  
 Ser Cys Glu Phe Pro Thr Cys Glu Pro Leu Thr Gln Phe Ile Cys Lys  
 965 970 975  
 Ser Gly Arg Cys Ile Ser Asn Lys Trp His Cys Asp Thr Asp Asp Asp  
 980 985 990  
 Cys Gly Asp Arg Ser Asp Glu Val Gly Cys Val His Ser Cys Leu Asp  
 995 1000 1005  
 Asp Gln Phe Arg Cys Ser Ser Gly Arg Cys Ile Pro Gly His Trp  
 1010 1015 1020  
 Ala Cys Asp Gly Asp Asn Asp Cys Gly Asp Phe Ser Asp Glu Thr  
 1025 1030 1035



## Nonprovisional IP-017.ST25.txt

His Ile Asn Cys Thr Lys Glu Glu Ala Arg Ser Pro Ala Gly Cys  
 1040 1045 1050  
 Ile Gly Asn Glu Phe Gln Cys Arg Pro Asp Gly Asn Cys Ile Pro  
 1055 1060 1065  
 Asp Leu Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Asp Gly Ser  
 1070 1075 1080  
 Asp Glu Lys Gly Cys Asn Gly Thr Ile Arg Leu Cys Asp His Lys  
 1085 1090 1095  
 Thr Lys Phe Ser Cys Arg Ser Thr Gly Arg Cys Ile Asn Asn Ala  
 1100 1105 1110  
 Trp Val Cys Asp Gly Asp Val Asp Cys Glu Asp Gln Ser Asp Glu  
 1115 1120 1125  
 Glu Asp Cys Asp Ser Phe Leu Cys Gly Pro Pro Lys Tyr Pro Cys  
 1130 1135 1140  
 Ala Asn Asp Thr Ser Val Cys Leu Gln Pro Glu Lys Leu Cys Asn  
 1145 1150 1155  
 Gly Arg Lys Asp Cys Pro Asp Gly Ser Asp Glu Gly Asp Leu Cys  
 1160 1165 1170  
 Asp Glu Cys Ser Leu Asn Asn Gly Gly Cys Ser Asn His Cys Ser  
 1175 1180 1185  
 Val Val Pro Gly Arg Gly Ile Val Cys Ser Cys Pro Glu Gly His  
 1190 1195 1200  
 Gln Leu Lys Lys Asp Asn Arg Thr Cys Glu Ile Val Asp Tyr Cys  
 1205 1210 1215  
 Ala Ser His Leu Arg Cys Ser Gln Val Cys Glu Gln Gln Lys His  
 1220 1225 1230  
 Met Val Lys Cys Ser Cys Tyr Glu Gly Trp Ala Leu Gly Thr Asp  
 1235 1240 1245  
 Gly Glu Ser Cys Thr Ser Val Asp Ser Phe Glu Ala Phe Ile Ile  
 1250 1255 1260  
 Phe Ser Ile Arg His Glu Ile Arg Arg Ile Asp Leu His Lys Gly  
 1265 1270 1275  
 Asp Tyr Ser Leu Leu Val Pro Gly Leu Arg Asn Thr Ile Ala Leu  
 1280 1285 1290

## Nonprovisional IP-017.ST25.txt

Asp Phe His Phe Asn Gln Ser Leu Leu Tyr Trp Thr Asp Val Val  
 1295 1300 1305  
 Glu Asp Arg Ile Tyr Arg Gly Lys Leu Ser Glu Ser Gly Gly Val  
 1310 1315 1320  
 Ser Ala Ile Glu Val Val Val Glu His Gly Leu Ala Thr Pro Glu  
 1325 1330 1335  
 Gly Leu Thr Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Ile Asp  
 1340 1345 1350  
 Ser Asn Leu Asp Gln Ile Glu Val Ser Lys Leu Asp Gly Ser Leu  
 1355 1360 1365  
 Arg Ala Thr Leu Ile Ala Gly Ala Met Glu His Pro Arg Ala Ile  
 1370 1375 1380  
 Ala Leu Asp Pro Arg Tyr Gly Ile Leu Phe Trp Thr Asp Trp Asp  
 1385 1390 1395  
 Ala Asn Phe Pro Arg Ile Glu Ser Ala Ser Met Ser Gly Ala Gly  
 1400 1405 1410  
 Arg Lys Thr Ile Tyr Lys Asp Met Lys Thr Gly Ala Trp Pro Asn  
 1415 1420 1425  
 Gly Leu Thr Val Asp His Phe Glu Arg Arg Ile Val Trp Thr Asp  
 1430 1435 1440  
 Ala Arg Ser Asp Ala Ile Tyr Ser Ala Phe Tyr Asp Gly Thr Asn  
 1445 1450 1455  
 Met Ile Glu Ile Ile Arg Gly His Glu Tyr Leu Ser His Pro Phe  
 1460 1465 1470  
 Ala Val Ser Leu Tyr Gly Ser Glu Val Tyr Trp Thr Asp Trp Arg  
 1475 1480 1485  
 Thr Asn Thr Leu Ala Lys Ala Asn Lys Trp Thr Gly Gln Asn Val  
 1490 1495 1500  
 Ser Val Ile Gln Lys Thr Ser Ala Gln Pro Phe Asp Leu Gln Ile  
 1505 1510 1515  
 Tyr His Pro Ser Arg Gln Pro Gln Ala Pro Asn Pro Cys Ala Ala  
 1520 1525 1530  
 Asn Glu Gly Arg Gly Pro Cys Ser His Leu Cys Leu Ile Asn His  
 1535 1540 1545

## Nonprovisional IP-017.ST25.txt

Asn Arg Ser Ala Ala Cys Ala Cys Pro His Leu Met Lys Leu Ser  
 1550 1555 1560  
 Ser Asp Lys Lys Thr Cys Tyr Glu Met Lys Lys Phe Leu Leu Tyr  
 1565 1570 1575  
 Ala Arg Arg Ser Glu Ile Arg Gly Val Asp Ile Asp Asn Pro Tyr  
 1580 1585 1590  
 Val Asn Phe Ile Thr Ala Phe Thr Val Pro Asp Ile Asp Asp Val  
 1595 1600 1605  
 Ala Val Ile Asp Phe Asp Ala Ser Glu Glu Arg Leu Tyr Trp Thr  
 1610 1615 1620  
 Asp Ile Lys Thr Gln Thr Ile Thr Arg Ala Phe Ile Asn Gly Thr  
 1625 1630 1635  
 Gly Leu Glu Thr Val Ile Ser Arg Asp Ile Gln Ser Ile Arg Gly  
 1640 1645 1650  
 Leu Ala Val Asp Trp Val Ser Arg Asn Leu Tyr Trp Ile Ser Ser  
 1655 1660 1665  
 Glu Phe Asp Glu Thr Gln Ile Asn Val Ala Arg Leu Asp Gly Ser  
 1670 1675 1680  
 Leu Lys Thr Ser Ile Ile His Gly Ile Asp Lys Pro Gln Cys Leu  
 1685 1690 1695  
 Ala Ala His Pro Val Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asn  
 1700 1705 1710  
 Thr Ile Asn Met Ala Asn Met Asp Gly Ser Asn Ser Lys Ile Leu  
 1715 1720 1725  
 Phe Gln Asn Gln Lys Glu Pro Val Gly Leu Ser Ile Asp Tyr Val  
 1730 1735 1740  
 Glu Asn Lys Leu Tyr Trp Ile Ser Ser Gly Asn Gly Thr Ile Asn  
 1745 1750 1755  
 Arg Cys Asn Leu Asp Gly Gly Asn Leu Glu Val Ile Glu Ser Met  
 1760 1765 1770  
 Lys Glu Glu Leu Thr Lys Ala Thr Ala Leu Thr Ile Met Asp Lys  
 1775 1780 1785  
 Lys Leu Trp Trp Ala Asp Gln Asn Leu Ala Gln Leu Gly Thr Cys  
 1790 1795 1800

## Nonprovisional IP-017.ST25.txt

Asn Lys Arg Asp Gly Arg Asn Pro Ser Ile Leu Arg Asn Lys Thr  
 1805 1810 1815  
 Ser Gly Val Val His Met Lys Val Tyr Asp Lys Glu Ala Gln Gln  
 1820 1825 1830  
 Gly Ser Asn Ser Cys Gln Val Asn Asn Gly Gly Cys Ser Gln Leu  
 1835 1840 1845  
 Cys Leu Pro Thr Ser Glu Thr Thr Arg Thr Cys Met Cys Thr Val  
 1850 1855 1860  
 Gly Tyr Tyr Leu Gln Lys Asn Arg Met Ser Cys Gln Gly Ile Glu  
 1865 1870 1875  
 Ser Phe Leu Met Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro  
 1880 1885 1890  
 Leu Glu Pro Arg Asp Lys Val Asp Ala Leu Met Pro Ile Ser Gly  
 1895 1900 1905  
 Ala Ala Phe Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr  
 1910 1915 1920  
 Ile Tyr Trp Thr Asp Met Gly Leu Asn Lys Ile Ser Arg Ala Lys  
 1925 1930 1935  
 Arg Asp Gln Thr Trp Lys Glu Asp Val Val Thr Asn Gly Leu Gly  
 1940 1945 1950  
 Arg Val Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr  
 1955 1960 1965  
 Trp Thr Asp His Gly Phe Asn Leu Ile Glu Val Ala Arg Leu Asn  
 1970 1975 1980  
 Gly Ser Phe Arg Tyr Val Ile Ile Ser Gln Gly Leu Asp Gln Pro  
 1985 1990 1995  
 Arg Ser Ile Ala Val His Pro Glu Lys Gly Phe Leu Phe Trp Thr  
 2000 2005 2010  
 Glu Trp Gly Gln Val Pro Cys Ile Gly Lys Ala Arg Leu Asp Gly  
 2015 2020 2025  
 Ser Glu Lys Val Met Ile Val Ser Val Gly Ile Thr Trp Pro Asn  
 2030 2035 2040  
 Gly Ile Ser Ile Asp Tyr Glu Glu Asn Lys Leu Tyr Trp Cys Asp  
 2045 2050 2055

## Nonprovisional IP-017.ST25.txt

Ala Arg Ser Asp Lys Ile Glu Arg Ile Asp Leu Asp Thr Gly Ala  
 2060 2065 2070  
 Asn Arg Glu Val Leu Leu Ser Gly Ser Asn Val Asp Leu Phe Ser  
 2075 2080 2085  
 Val Ala Val Phe Gly Ala Tyr Ile Tyr Trp Ser Asp Arg Ala His  
 2090 2095 2100  
 Ala Asn Gly Ser Val Arg Arg Gly His Lys Asn Asp Ala Thr Glu  
 2105 2110 2115  
 Thr Val Thr Met Arg Thr Gly Leu Gly Val Asn Leu Lys Glu Ile  
 2120 2125 2130  
 Lys Ile Phe Asn Arg Val Arg Glu Lys Gly Thr Asn Val Cys Ala  
 2135 2140 2145  
 Lys Glu Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Asn  
 2150 2155 2160  
 Ser Arg Arg Thr Cys Ala Cys Ala His Gly Tyr Leu Ala Gly Asp  
 2165 2170 2175  
 Gly Val Thr Cys Leu Arg His Glu Gly Tyr Leu Leu Tyr Ser Gly  
 2180 2185 2190  
 Arg Thr Ile Leu Lys Ser Ile His Leu Ser Asp Glu Thr Asn Leu  
 2195 2200 2205  
 Asn Ser Pro Val Arg Pro Tyr Glu Asn Pro Asn Tyr Phe Lys Asn  
 2210 2215 2220  
 Ile Ile Ala Leu Ala Phe Asp Tyr Asn Gln Arg Arg Glu Gly Thr  
 2225 2230 2235  
 Asn Arg Ile Phe Tyr Ser Asp Ala His Phe Gly Asn Ile Gln Leu  
 2240 2245 2250  
 Ile Lys Asp Asn Trp Glu Asp Arg Gln Val Ile Val Glu Asn Val  
 2255 2260 2265  
 Gly Ser Val Glu Gly Leu Ala Tyr His Arg Ala Trp Asp Thr Leu  
 2270 2275 2280  
 Tyr Trp Thr Ser Ser Ser Thr Ser Ser Ile Thr Arg His Thr Val  
 2285 2290 2295  
 Asp Gln Thr Arg Pro Gly Ala Ile Asp Arg Glu Ala Val Ile Thr  
 2300 2305 2310

## Nonprovisional IP-017.ST25.txt

Met Ser Glu Asp Asp His Pro His Val Leu Ala Leu Asp Glu Cys  
 2315 2320 2325  
 Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His Pro Ser  
 2330 2335 2340  
 Ile Met Arg Ala Thr Leu Thr Gly Lys Asn Ala His Val Val Val  
 2345 2350 2355  
 Ser Thr Asp Ile Leu Thr Pro Asn Gly Leu Thr Ile Asp His Arg  
 2360 2365 2370  
 Ala Glu Lys Leu Tyr Phe Ser Asp Gly Ser Leu Gly Lys Ile Glu  
 2375 2380 2385  
 Arg Cys Glu Tyr Asp Gly Ser Gln Arg His Val Ile Val Lys Ser  
 2390 2395 2400  
 Gly Pro Gly Thr Phe Leu Ser Leu Ala Val Tyr Asp Ser Tyr Ile  
 2405 2410 2415  
 Phe Trp Ser Asp Trp Gly Arg Arg Ala Ile Leu Arg Ser Asn Lys  
 2420 2425 2430  
 Tyr Thr Gly Gly Glu Thr Lys Ile Leu Arg Ser Asp Ile Pro His  
 2435 2440 2445  
 Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys  
 2450 2455 2460  
 Glu Leu Ser Pro Cys Ala Leu Leu Asn Gly Gly Cys His Asp Leu  
 2465 2470 2475  
 Cys Leu Leu Thr Pro Asp Gly Arg Val Asn Cys Ser Cys Arg Gly  
 2480 2485 2490  
 Asp Arg Val Leu Leu Ala Asn Asn Arg Cys Val Thr Lys Asn Ser  
 2495 2500 2505  
 Ser Cys Asn Ile Tyr Ser Glu Phe Glu Cys Gly Asn Gly Asp Cys  
 2510 2515 2520  
 Val Asp Tyr Val Leu Thr Cys Asp Gly Ile Pro His Cys Lys Asp  
 2525 2530 2535  
 Lys Ser Asp Glu Lys Leu Leu Tyr Cys Glu Asn Arg Ser Cys Arg  
 2540 2545 2550  
 Ser Gly Phe Lys Pro Cys Tyr Asn Arg Arg Cys Val Pro His Gly  
 2555 2560 2565

## Nonprovisional IP-017.ST25.txt

Lys Leu Cys Asp Gly Thr Asn Asp Cys Gly Asp Ser Ser Asp Glu  
 2570 2575 2580  
 Leu Asp Cys Lys Val Ser Thr Cys Ser Thr Val Glu Phe Arg Cys  
 2585 2590 2595  
 Ala Asp Gly Thr Cys Ile Pro Arg Ser Ala Arg Cys Asn Gln Asn  
 2600 2605 2610  
 Met Asp Cys Ser Asp Ala Ser Asp Glu Lys Gly Cys Asn Asn Thr  
 2615 2620 2625  
 Asp Cys Thr His Phe Tyr Lys Leu Gly Val Lys Ser Thr Gly Phe  
 2630 2635 2640  
 Ile Arg Cys Asn Ser Thr Ser Leu Cys Val Leu Pro Ser Trp Ile  
 2645 2650 2655  
 Cys Asp Gly Ser Asn Asp Cys Gly Asp Tyr Ser Asp Glu Leu Lys  
 2660 2665 2670  
 Cys Pro Val Gln Asn Lys His Lys Cys Glu Glu Asn Tyr Phe Gly  
 2675 2680 2685  
 Cys Pro Ser Gly Arg Cys Ile Leu Asn Thr Trp Val Cys Asp Gly  
 2690 2695 2700  
 Gln Lys Asp Cys Glu Asp Gly Leu Asp Glu Leu His Cys Asp Ser  
 2705 2710 2715  
 Ser Cys Ser Trp Asn Gln Phe Ala Cys Ser Val Lys Lys Cys Ile  
 2720 2725 2730  
 Ser Lys His Trp Ile Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser  
 2735 2740 2745  
 Leu Asp Glu Ser Asp Ser Ile Cys Gly Ala Val Thr Cys Ala Ala  
 2750 2755 2760  
 Asp Met Phe Ser Cys Gln Gly Ser His Ala Cys Val Pro Gln His  
 2765 2770 2775  
 Trp Leu Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu  
 2780 2785 2790  
 Leu Ser Ser Ala Gly Cys Ala Pro Asn Asn Thr Cys Asp Glu Asn  
 2795 2800 2805  
 Ala Phe Met Cys His Asn Lys Val Cys Ile Pro Lys Gln Phe Val  
 2810 2815 2820

## Nonprovisional IP-017.ST25.txt

Cys Asp His Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu Phe Leu  
 2825 2830 2835  
 Gln Cys Gly Tyr Arg Gln Cys Gly Pro Glu Glu Phe Arg Cys Ala  
 2840 2845 2850  
 Asp Gly Arg Cys Leu Val Asn Thr Leu Trp Gln Cys Asp Gly Asp  
 2855 2860 2865  
 Phe Asp Cys Pro Asp Ser Ser Asp Glu Ala Pro Ile Asn Pro Arg  
 2870 2875 2880  
 Cys Arg Ser Ala Glu His Ser Cys Asn Ser Ser Phe Phe Met Cys  
 2885 2890 2895  
 Lys Asn Gly Arg Cys Ile Pro Ser Asp Gly Leu Cys Asp Ile Arg  
 2900 2905 2910  
 Asp Asp Cys Gly Asp Gly Ser Asp Glu Thr Asn Cys His Ile Asn  
 2915 2920 2925  
 Glu Cys Leu Ser Lys Lys Ile Ser Gly Cys Ser Gln Asp Cys Gln  
 2930 2935 2940  
 Asp Leu Pro Val Ser Tyr Lys Cys Lys Cys Trp Pro Gly Phe Gln  
 2945 2950 2955  
 Leu Lys Asp Asp Gly Lys Thr Cys Val Asp Ile Asp Glu Cys Ser  
 2960 2965 2970  
 Ser Gly Phe Pro Cys Ser Gln Gln Cys Ile Asn Thr Tyr Gly Thr  
 2975 2980 2985  
 Tyr Lys Cys His Cys Ala Glu Gly Tyr Glu Thr Gln Pro Asp Asn  
 2990 2995 3000  
 Pro Asn Gly Cys Arg Ser Leu Ser Asp Glu Glu Pro Phe Leu Ile  
 3005 3010 3015  
 Leu Ala Asp Gln His Glu Ile Arg Lys Ile Ser Thr Asp Gly Ser  
 3020 3025 3030  
 Asn Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Val Ile Ala Leu  
 3035 3040 3045  
 Asp Phe Asp Tyr Arg Glu Glu Phe Ile Tyr Trp Ile Asp Ser Ser  
 3050 3055 3060  
 Arg Pro Asn Gly Ser Arg Ile Asn Arg Met Cys Leu Asn Gly Ser  
 3065 3070 3075



## Nonprovisional IP-017.ST25.txt

Asp Ile Lys Val Val His Asn Thr Ala Val Pro Asn Ala Leu Ala  
 3080 3085 3090  
 Val Asp Trp Ile Gly Lys Asn Leu Tyr Trp Ser Asp Thr Glu Lys  
 3095 3100 3105  
 Arg Ile Ile Glu Val Ser Lys Leu Asn Gly Leu Tyr Pro Thr Val  
 3110 3115 3120  
 Leu Val Ser Lys Arg Leu Lys Phe Pro Arg Asp Leu Ser Leu Asp  
 3125 3130 3135  
 Pro Arg Ala Gly Asn Leu Tyr Trp Ile Asp Cys Cys Glu Tyr Pro  
 3140 3145 3150  
 His Ile Gly Arg Val Gly Met Asp Gly Thr Asn Gln Ser Val Val  
 3155 3160 3165  
 Ile Glu Thr Lys Ile Ser Arg Pro Met Ala Leu Thr Ile Asp Tyr  
 3170 3175 3180  
 Val Asn His Arg Leu Tyr Trp Ala Asp Glu Asn His Ile Glu Phe  
 3185 3190 3195  
 Ser Asn Met Asp Gly Ser His Arg His Lys Val Pro Asn Gln Asp  
 3200 3205 3210  
 Ile Pro Gly Val Ile Ala Leu Thr Leu Phe Glu Asp Tyr Ile Tyr  
 3215 3220 3225  
 Trp Thr Asp Gly Lys Thr Lys Ser Leu Ser Arg Val His Lys Thr  
 3230 3235 3240  
 Ser Gly Ala Asp Arg Leu Ser Leu Ile Asn Ser Trp His Ala Ile  
 3245 3250 3255  
 Thr Asp Ile Gln Val Tyr His Ser Tyr Arg Gln Pro Asp Val Ser  
 3260 3265 3270  
 Lys His Leu Cys Thr Val Asn Asn Gly Gly Cys Ser His Leu Cys  
 3275 3280 3285  
 Leu Leu Gly Pro Gly Lys Thr His Thr Cys Ala Cys Pro Thr Asn  
 3290 3295 3300  
 Phe Tyr Leu Ala Ala Asp Asn Arg Thr Cys Leu Ser Asn Cys Thr  
 3305 3310 3315  
 Ala Ser Gln Phe Arg Cys Lys Thr Asp Lys Cys Ile Pro Phe Trp  
 3320 3325 3330

## Nonprovisional IP-017.ST25.txt

Trp Lys Cys Asp Thr Val Asp Asp Cys Gly Asp Gly Ser Asp Glu  
 3335 3340 3345  
 Pro Asp Asp Cys Pro Glu Phe Lys Cys Gln Pro Gly Arg Phe Gln  
 3350 3355 3360  
 Cys Gly Thr Gly Leu Cys Ala Leu Pro Ala Phe Ile Cys Asp Gly  
 3365 3370 3375  
 Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu Leu Asn Cys Asp Thr  
 3380 3385 3390  
 His Val Cys Leu Ala Gly Gln Phe Lys Cys Thr Lys Asn Lys Lys  
 3395 3400 3405  
 Cys Ile Pro Val Asn Leu Arg Cys Asn Gly Gln Asp Asp Cys Gly  
 3410 3415 3420  
 Asp Glu Glu Asp Glu Lys Asp Cys Pro Glu Asn Ser Cys Ser Pro  
 3425 3430 3435  
 Asp Tyr Phe Gln Cys Lys Thr Thr Lys His Cys Ile Ser Lys Leu  
 3440 3445 3450  
 Trp Val Cys Asp Glu Asp Pro Asp Cys Ala Asp Ala Ser Asp Glu  
 3455 3460 3465  
 Ala Asn Cys Asp Lys Lys Thr Cys Gly Pro His Glu Phe Gln Cys  
 3470 3475 3480  
 Lys Asn Asn Asn Cys Ile Pro Asp His Trp Arg Cys Asp Asn Gln  
 3485 3490 3495  
 Asn Asp Cys Ser Asp Asn Ser Asp Glu Asp Asn Cys Lys Pro Gln  
 3500 3505 3510  
 Thr Cys Thr Leu Lys Asp Phe Leu Cys Ser Asn Gly Asp Cys Val  
 3515 3520 3525  
 Ser Ser Arg Phe Trp Cys Asp Gly Glu Phe Asp Cys Ala Asp Gly  
 3530 3535 3540  
 Ser Asp Glu Lys Asn Cys Glu Thr Ser Cys Ser Lys Asp Gln Phe  
 3545 3550 3555  
 Gln Cys Ser Asn Gly Gln Cys Leu Ser Ala Lys Trp Lys Cys Asp  
 3560 3565 3570  
 Gly His Glu Asp Cys Lys Tyr Gly Glu Asp Glu Lys Asn Cys Glu  
 3575 3580 3585

## Nonprovisional IP-017.ST25.txt

Pro Ala Phe Pro Val Cys Ser Ser Ser Glu Tyr Met Cys Ala Ser  
 3590 3595 3600  
 Gly Gly Cys Leu Ser Ala Ser Leu Lys Cys Asn Gly Glu Pro Asp  
 3605 3610 3615  
 Cys Val Asp Gly Ser Asp Glu Met Asp Cys Val Ile Glu Cys Lys  
 3620 3625 3630  
 Glu Asp Gln Phe Gln Cys Lys Asn Lys Ala Tyr Cys Ile Pro Ile  
 3635 3640 3645  
 Arg Trp Leu Cys Asp Gly Ile Tyr Asp Cys Val Asp Gly Ser Asp  
 3650 3655 3660  
 Glu Glu Thr Cys Gly Arg Gly Gly Ser Ile Cys Arg Asp Asp Glu  
 3665 3670 3675  
 Phe Leu Cys Asn Asn Ser Leu Cys Lys Leu His Phe Trp Val Cys  
 3680 3685 3690  
 Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu Ala Pro Asp  
 3695 3700 3705  
 Met Cys Val Lys Phe Leu Cys Pro Pro Thr Arg Pro Tyr Arg Cys  
 3710 3715 3720  
 Arg Asn Asp Arg Ile Cys Leu Gln Leu Glu Lys Ile Cys Asn Gly  
 3725 3730 3735  
 Ile Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu His Cys Ser Gly  
 3740 3745 3750  
 Lys Leu Ser Leu Lys Ser Lys Pro Cys Lys Lys Asp Glu Phe Thr  
 3755 3760 3765  
 Cys Ser Asn Arg Asn Cys Ile Pro Met Glu Leu Gln Cys Asp Ser  
 3770 3775 3780  
 Leu Asp Asp Cys Gly Asp Gly Ser Asp Glu Gln Gly Cys Leu Lys  
 3785 3790 3795  
 Thr Pro Ile Glu His Thr Cys Glu Asn Asn Gly Asn Pro Cys Gly  
 3800 3805 3810  
 Asp Asp Ala Tyr Cys Asn Gln Ile Lys Thr Ser Val Phe Cys Arg  
 3815 3820 3825  
 Cys Lys Pro Gly Phe Gln Arg Asn Met Lys Gly Arg Glu Cys Ala  
 3830 3835 3840

## Nonprovisional IP-017.ST25.txt

Asp Leu Asn Glu Cys Leu Leu Phe Gly Ile Cys Ser His His Cys  
 3845 3850 3855  
 Leu Asn Thr Arg Gly Ser Tyr Lys Cys Val Cys Asp Gln Asn Phe  
 3860 3865 3870  
 Gln Glu Lys Asn Asn Ser Cys Ile Ala Lys Gly Ser Glu Asp Gln  
 3875 3880 3885  
 Ala Leu Tyr Ile Ala Asn Asp Thr Asp Ile Leu Gly Phe Val Tyr  
 3890 3895 3900  
 Pro Phe Asn Tyr Ser Gly Gly His Gln Gln Ile Ser His Val Glu  
 3905 3910 3915  
 His Asn Ser Arg Ile Thr Gly Met Asp Val His Tyr Gln Arg Asn  
 3920 3925 3930  
 Val Ile Val Trp Ser Thr Gln Phe Asn Pro Gly Gly Ile Phe Tyr  
 3935 3940 3945  
 Lys Met Ile Asp Ala Arg Glu Lys Arg Gln Ala Asn Ser Gly Leu  
 3950 3955 3960  
 Ile Cys Pro Glu Phe Lys Arg Pro Arg Asp Ile Ala Val Asp Trp  
 3965 3970 3975  
 Val Ala Gly Asn Val Tyr Trp Thr Asp His Ser Arg Met His Trp  
 3980 3985 3990  
 Phe Ser Tyr Tyr Thr Thr His Trp Thr Ser Leu Arg Tyr Ser Ile  
 3995 4000 4005  
 Asn Val Gly Gln Leu Asn Gly Pro Asn Cys Thr Arg Leu Leu Thr  
 4010 4015 4020  
 Asn Met Ala Gly Glu Pro Tyr Ala Ile Ala Val Asn Pro Lys Arg  
 4025 4030 4035  
 Gly Met Met Tyr Trp Thr Val Ile Gly Asp His Ser His Ile Glu  
 4040 4045 4050  
 Glu Ala Ala Met Asp Gly Thr Leu Arg Arg Val Leu Val Gln Lys  
 4055 4060 4065  
 Asn Leu Gln Arg Pro Thr Gly Leu Thr Val Asp His Phe Gly Glu  
 4070 4075 4080  
 Arg Ile Tyr Trp Ala Asp Phe Glu Leu Ser Ile Ile Gly Ser Val  
 4085 4090 4095

## Nonprovisional IP-017.ST25.txt

Leu Tyr Asp Gly Ser Ser Pro Val Val Ser Val Ser Ser Lys Gln  
 4100 4105 4110  
 Gly Leu Leu His Pro His Arg Ile Asp Val Phe Glu Asp Tyr Ile  
 4115 4120 4125  
 Tyr Gly Ala Gly Pro Lys Asn Gly Ile Phe Arg Val Gln Lys Phe  
 4130 4135 4140  
 Gly His Gly Ser Val Glu Val Leu Ala Leu Gly Val Asp Lys Thr  
 4145 4150 4155  
 Lys Ser Ile Leu Val Ser His Arg Tyr Lys Gln Leu Asn Leu Pro  
 4160 4165 4170  
 Asn Pro Cys Leu Asp Leu Ser Cys Asp Phe Leu Cys Leu Leu Asn  
 4175 4180 4185  
 Pro Ser Gly Ala Thr Cys Ile Cys Pro Glu Gly Lys Tyr Met Met  
 4190 4195 4200  
 Asn Gly Thr Cys His Asp Asp Ser Leu Leu Asp Asp Ser Cys Lys  
 4205 4210 4215  
 Leu Thr Cys Glu Asn Gly Gly Arg Cys Ile Leu Asn Glu Lys Gly  
 4220 4225 4230  
 Asp Leu Arg Cys His Cys Trp Pro Ser Tyr Ser Gly Gly Arg Cys  
 4235 4240 4245  
 Glu Val Asn His Cys Ser Asn Tyr Cys Gln Asn Gly Gly Thr Cys  
 4250 4255 4260  
 Ile Pro Ser Thr Leu Gly Arg Pro Thr Cys Ile Cys Ala Leu Gly  
 4265 4270 4275  
 Phe Thr Gly Pro Asn Cys Gly Lys Ala Val Cys Glu Asp Ser Cys  
 4280 4285 4290  
 His Asn Gly Gly Ser Cys Val Val Thr Ala Gly Asn Gln Pro Tyr  
 4295 4300 4305  
 Cys His Cys Gln Ala Asp Tyr Thr Gly Asp Arg Cys Gln Tyr Tyr  
 4310 4315 4320  
 Val Cys His His Tyr Cys Val Asn Ser Glu Ser Cys Thr Ile Gly  
 4325 4330 4335  
 Asn Asp Gly Ser Val Glu Cys Val Cys Pro Thr Arg Tyr Glu Gly  
 4340 4345 4350

## Nonprovisional IP-017.ST25.txt

Pro Lys Cys Glu Ile Asp Lys Cys Val Arg Cys His Gly Gly His  
 4355 4360 4365  
 Cys Ile Ile Asn Lys Asp Asn Glu Asp Ile Phe Cys Asn Cys Thr  
 4370 4375 4380  
 Asn Gly Lys Ile Ala Ser Ser Cys Gln Leu Cys Asp Gly Tyr Cys  
 4385 4390 4395  
 Tyr Asn Gly Gly Thr Cys Gln Leu Asp Pro Glu Thr Ser Ile Pro  
 4400 4405 4410  
 Val Cys Val Cys Ser Thr Asn Trp Ser Gly Thr Gln Cys Glu Arg  
 4415 4420 4425  
 Pro Ala Pro Lys Ser Ser Lys Ser Glu His Ile Ser Thr Arg Ser  
 4430 4435 4440  
 Ile Ala Ile Ile Val Pro Leu Val Leu Leu Val Thr Leu Val Thr  
 4445 4450 4455  
 Thr Leu Val Ile Gly Leu Val Val Cys Lys Arg Lys Arg Arg Thr  
 4460 4465 4470  
 Lys Thr Ile Arg Arg Gln Pro Ile Ile Asn Gly Gly Ile Asn Val  
 4475 4480 4485  
 Glu Ile Gly Asn Pro Ser Tyr Asn Met Tyr Glu Val Asp His Asp  
 4490 4495 4500  
 His Ser Asp Gly Gly Leu Leu Glu Pro Ser Phe Met Ile Asp Pro  
 4505 4510 4515  
 Val Lys Ser Arg Tyr Ile Gly Gly Gly Ser Ser Ala Phe Lys Leu  
 4520 4525 4530  
 Pro His Thr Ala Pro Pro Ile Tyr Leu Asn Ser Asp Leu Lys Gly  
 4535 4540 4545  
 Pro Leu Thr Phe Gly Pro Thr Asn Tyr Ser Asn Pro Val Tyr Ala  
 4550 4555 4560  
 Lys Leu Tyr Met Asp Gly Gln Asn Cys Arg Asn Ser Leu Ala Ser  
 4565 4570 4575  
 Val Asp Glu Arg Lys Glu Leu Leu Pro Lys Lys Ile Glu Ile Gly  
 4580 4585 4590  
 Ile Arg Glu Thr Val Ala  
 4595

## Nonprovisional IP-017.ST25.txt

<210> 70  
 <211> 4599  
 <212> PRT  
 <213> MOUSE

<400> 70

Met Ser Gln Leu Leu Leu Ala Ile Leu Thr Leu Ser Gly Leu Leu Pro  
 1 5 10 15

Asn Ala Glu Val Leu Ile Val Gly Ala Asn Gln Asp Gln His Leu Cys  
 20 25 30

Asp Pro Gly Glu Phe Leu Cys His Asp His Val Thr Cys Val Ser Gln  
 35 40 45

Ser Trp Leu Cys Asp Gly Asp Pro Asp Cys Pro Asp Gln Ser Asp Glu  
 50 55 60

Ser Leu Asp Thr Cys Pro Glu Glu Val Glu Ile Lys Cys Pro Leu Asn  
 65 70 75 80

His Ile Ala Cys His Gly Ser Ser Ala Cys Val His Leu Ser Lys Leu  
 85 90 95

Cys Asn Gly Val Val Asp Cys Pro Asp Gly Phe Asp Glu Gly Gly His  
 100 105 110

Cys Gln Glu Leu Leu Pro Ser Cys Gln Gln Leu Asn Cys Gln Phe Lys  
 115 120 125

Cys Ala Met Val Arg Asn Ala Thr Arg Cys Tyr Cys Glu Asp Gly Phe  
 130 135 140

Glu Val Ala Glu Asp Gly Arg Ser Cys Lys Asp Gln Asp Glu Cys Ser  
 145 150 155 160

Ile Tyr Gly Ile Cys Ser Gln Thr Cys Lys Asn Thr Tyr Gly Ser Tyr  
 165 170 175

Ala Cys Ser Cys Val Glu Gly Tyr Ile Met Gln Ser Asp Asn Arg Ser  
 180 185 190

Cys Lys Val Lys His Glu Pro Thr Asp Lys Ala Pro Met Leu Leu Ile  
 195 200 205

Ser Ser Leu Glu Thr Ile Glu Leu Phe Tyr Ile Asn Gly Ser Lys Met  
 210 215 220

Thr Thr Leu Ser Ser Ala Asn Arg Asn Glu Ile His Thr Leu Asp Phe  
 225 230 235 240

## Nonprovisional IP-017.ST25.txt

Ile Tyr Ser Glu Glu Met Ile Cys Trp Ile Glu Ser Arg Glu Ser Ser  
 245 250 255  
 Asn Gln Leu Lys Cys Gly Gln Ile Thr Lys Ala Gly Arg Leu Thr Asp  
 260 265 270  
 Gln Arg Ile Ile Asn Ser Leu Gln Ser Phe Gln Asn Val Glu Gln Met  
 275 280 285  
 Ala Phe Asp Trp Leu Thr Arg Asn Ile Tyr Phe Val Asp His Val Ser  
 290 295 300  
 Asp Arg Ile Phe Val Cys Asn Phe Asn Gly Ser Val Cys Val Thr Leu  
 305 310 315 320  
 Ile Glu Ser Glu Leu His Asn Pro Lys Ala Ile Ala Ala Asp Pro Ile  
 325 330 335  
 Ala Gly Lys Leu Phe Phe Thr Asp Tyr Gly Asn Val Pro Lys Ile Glu  
 340 345 350  
 Arg Cys Asp Leu Asp Gly Met Asn Arg Thr Arg Ile Val Tyr Ser Lys  
 355 360 365  
 Ala Glu Gln Pro Ser Ala Leu Ala Leu Asp Leu Val Asn Arg Leu Val  
 370 375 380  
 Tyr Trp Val Asp Leu Tyr Leu Asp Tyr Val Gly Val Val Asp Tyr Gln  
 385 390 395 400  
 Gly Lys Asn Arg His Thr Ile Val Gln Gly Arg Gln Val Lys His Leu  
 405 410 415  
 Tyr Gly Ile Thr Val Phe Glu Asp Tyr Leu Tyr Ala Thr Ser Ser Asp  
 420 425 430  
 Asn Phe Asn Ile Ile Arg Ile Asn Arg Phe Asn Gly Thr Asp Ile His  
 435 440 445  
 Ser Ile Ile Lys Met Glu Ser Ala Arg Gly Ile Arg Thr Tyr Gln Lys  
 450 455 460  
 Arg Thr Gln Pro Thr Val Arg Ser His Ala Cys Glu Val Asp Ala Tyr  
 465 470 475 480  
 Gly Met Pro Gly Gly Cys Ser His Ile Cys Leu Leu Ser Ser Ser Tyr  
 485 490 495  
 Lys Thr Arg Thr Cys Arg Cys Arg Thr Gly Phe Asn Met Gly Ser Asp  
 500 505 510



## Nonprovisional IP-017.ST25.txt

Gly Arg Ser Cys Lys Arg Pro Lys Asn Glu Leu Phe Leu Phe Tyr Gly  
 515 520 525  
 Lys Gly Arg Pro Gly Ile Val Arg Gly Met Asp Leu Asn Thr Lys Ile  
 530 535 540  
 Ala Asp Glu Cys Met Ile Pro Ile Glu Asn Leu Val Asn Pro Arg Ala  
 545 550 555 560  
 Leu Asp Phe His Ala Glu Ala Asn Tyr Ile Tyr Phe Ala Asp Thr Thr  
 565 570 575  
 Ser Phe Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu Arg Glu Thr  
 580 585 590  
 Ile Leu Lys Asp Asp Leu Asp Asn Val Glu Gly Ile Ala Val Asp Trp  
 595 600 605  
 Ile Gly Asn Asn Leu Tyr Trp Thr Asn Asp Gly His Arg Lys Thr Ile  
 610 615 620  
 Asn Val Ala Arg Leu Glu Lys Ala Ser Gln Ser Arg Lys Thr Leu Leu  
 625 630 635 640  
 Glu Gly Gly Met Ser His Pro Arg Ala Ile Val Val Asp Pro Val Asn  
 645 650 655  
 Gly Trp Met Tyr Trp Thr Asp Trp Lys Glu Asp Lys Ile Asp Asp Ser  
 660 665 670  
 Val Gly Arg Ile Glu Lys Ala Trp Met Asp Gly Val Asn Arg Gln Val  
 675 680 685  
 Phe Val Thr Ser Lys Met Leu Trp Pro Asn Gly Leu Thr Leu Asp Phe  
 690 695 700  
 His Thr Ser Thr Leu Tyr Trp Cys Asp Ala Tyr Tyr Asp His Ile Glu  
 705 710 715 720  
 Lys Val Phe Leu Asn Gly Thr His Arg Lys Val Val Tyr Ser Gly Lys  
 725 730 735  
 Glu Leu Asn His Pro Phe Gly Leu Ser His His Gly Asn Tyr Val Phe  
 740 745 750  
 Trp Thr Asp Tyr Met Asn Gly Ser Ile Phe Gln Leu Asp Leu Met Thr  
 755 760 765  
 Asn Glu Val Thr Leu Leu Arg His Glu Arg Ala Pro Leu Phe Gly Leu  
 770 775 780

## Nonprovisional IP-017.ST25.txt

Gln Ile Tyr Asp Pro Arg Lys Gln Gln Gly Asp Asn Met Cys Arg Ile  
 785 790 795 800  
 Asn Asn Gly Gly Cys Gly Thr Leu Cys Leu Ala Ile Pro Ala Gly Arg  
 805 810 815  
 Val Cys Ala Cys Ala Asp Asn Gln Leu Leu Asp Glu Asn Gly Thr Thr  
 820 825 830  
 Cys Thr Phe Asn Pro Glu Glu Ile Arg Phe His Ile Cys Lys Pro Gly  
 835 840 845  
 Glu Phe Arg Cys Lys Asn Lys His Cys Ile Gln Ala Arg Trp Lys Cys  
 850 855 860  
 Asp Gly Asp Asp Asp Cys Leu Asp Gly Ser Asp Glu Asp Ser Val Thr  
 865 870 875 880  
 Cys Phe Asn His Ser Cys Pro Asp Asp Gln Phe Lys Cys Gln Asn Asn  
 885 890 895  
 Arg Cys Ile Pro Lys Arg Trp Leu Cys Asp Gly Ala Asn Asp Cys Gly  
 900 905 910  
 Ser Asn Glu Asp Glu Ser Asn Gln Thr Cys Thr Ala Arg Thr Cys Gln  
 915 920 925  
 Ala Asp Gln Phe Ser Cys Gly Asn Gly Arg Cys Ile Pro Thr Ala Trp  
 930 935 940  
 Leu Cys Asp Arg Glu Asp Asp Cys Gly Asp Gln Thr Asp Glu Val Ala  
 945 950 955 960  
 Ser Cys Glu Phe Pro Thr Cys Glu Pro Leu Thr Gln Phe Ile Cys Lys  
 965 970 975  
 Ser Gly Arg Cys Ile Ser Asn Lys Trp His Cys Asp Thr Asp Asp Asp  
 980 985 990  
 Cys Gly Asp Arg Ser Asp Glu Val Gly Cys Val His Ser Cys Leu Asp  
 995 1000 1005  
 Asp Gln Phe Arg Cys Ser Ser Gly Arg Cys Ile Pro Gly His Trp  
 1010 1015 1020  
 Ala Cys Asp Gly Asp Asn Asp Cys Gly Asp Phe Ser Asp Glu Thr  
 1025 1030 1035  
 His Ile Asn Cys Thr Lys Glu Glu Ala Arg Ser Pro Ala Gly Cys  
 1040 1045 1050

## Nonprovisional IP-017.ST25.txt

Ile Gly Asn Glu Phe Gln Cys Arg Pro Asp Gly Asn Cys Ile Pro  
 1055 1060 1065  
 Asp Leu Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Asp Gly Ser  
 1070 1075 1080  
 Asp Glu Lys Gly Cys Asn Gly Thr Ile Arg Leu Cys Asp His Lys  
 1085 1090 1095  
 Thr Lys Phe Ser Cys Arg Ser Thr Gly Arg Cys Ile Asn Asn Ala  
 1100 1105 1110  
 Trp Val Cys Asp Gly Asp Val Asp Cys Glu Asp Gln Ser Asp Glu  
 1115 1120 1125  
 Glu Asp Cys Asp Ser Phe Leu Cys Gly Pro Pro Lys Tyr Pro Cys  
 1130 1135 1140  
 Ala Asn Asp Thr Ser Val Cys Leu Gln Pro Glu Lys Leu Cys Asn  
 1145 1150 1155  
 Gly Arg Lys Asp Cys Pro Asp Gly Ser Asp Glu Gly Asp Leu Cys  
 1160 1165 1170  
 Asp Glu Cys Ser Leu Asn Asn Gly Gly Cys Ser Asn His Cys Ser  
 1175 1180 1185  
 Val Val Pro Gly Arg Gly Ile Val Cys Ser Cys Pro Glu Gly His  
 1190 1195 1200  
 Gln Leu Lys Lys Asp Asn Arg Thr Cys Glu Ile Val Asp Tyr Cys  
 1205 1210 1215  
 Ala Ser His Leu Arg Cys Ser Gln Val Cys Glu Gln Gln Lys His  
 1220 1225 1230  
 Met Val Lys Cys Ser Cys Tyr Glu Gly Trp Ala Leu Gly Thr Asp  
 1235 1240 1245  
 Gly Glu Ser Cys Thr Ser Val Asp Ser Phe Glu Ala Phe Ile Ile  
 1250 1255 1260  
 Phe Ser Ile Arg His Glu Ile Arg Arg Ile Asp Leu His Lys Gly  
 1265 1270 1275  
 Asp Tyr Ser Leu Leu Val Pro Gly Leu Arg Asn Thr Ile Ala Leu  
 1280 1285 1290  
 Asp Phe His Phe Asn Gln Ser Leu Leu Tyr Trp Thr Asp Val Val  
 1295 1300 1305

## Nonprovisional IP-017.ST25.txt

Glu Asp Arg Ile Tyr Arg Gly Lys Leu Ser Glu Ser Gly Gly Val  
 1310 1315 1320  
 Ser Ala Ile Glu Val Val Val Glu His Gly Leu Ala Thr Pro Glu  
 1325 1330 1335  
 Gly Leu Thr Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Ile Asp  
 1340 1345 1350  
 Ser Asn Leu Asp Gln Ile Glu Val Ser Lys Leu Asp Gly Ser Leu  
 1355 1360 1365  
 Arg Ala Thr Leu Ile Ala Gly Ala Met Glu His Pro Arg Ala Ile  
 1370 1375 1380  
 Ala Leu Asp Pro Arg Tyr Gly Ile Leu Phe Trp Thr Asp Trp Asp  
 1385 1390 1395  
 Ala Asn Phe Pro Arg Ile Glu Ser Ala Ser Met Ser Gly Ala Gly  
 1400 1405 1410  
 Arg Lys Thr Ile Tyr Lys Asp Met Lys Thr Gly Ala Trp Pro Asn  
 1415 1420 1425  
 Gly Leu Thr Val Asp His Phe Glu Arg Arg Ile Val Trp Thr Asp  
 1430 1435 1440  
 Ala Arg Ser Asp Ala Ile Tyr Ser Ala Phe Tyr Asp Gly Thr Asn  
 1445 1450 1455  
 Met Ile Glu Ile Ile Arg Gly His Glu Tyr Leu Ser His Pro Phe  
 1460 1465 1470  
 Ala Val Ser Leu Tyr Gly Ser Glu Val Tyr Trp Thr Asp Trp Arg  
 1475 1480 1485  
 Thr Asn Thr Leu Ala Lys Ala Asn Lys Trp Thr Gly Gln Asn Val  
 1490 1495 1500  
 Ser Val Ile Gln Lys Thr Ser Ala Gln Pro Phe Asp Leu Gln Ile  
 1505 1510 1515  
 Tyr His Pro Ser Arg Gln Pro Gln Ala Pro Asn Pro Cys Ala Ala  
 1520 1525 1530  
 Asn Glu Gly Arg Gly Pro Cys Ser His Leu Cys Leu Ile Asn His  
 1535 1540 1545  
 Asn Arg Ser Ala Ala Cys Ala Cys Pro His Leu Met Lys Leu Ser  
 1550 1555 1560

## Nonprovisional IP-017.ST25.txt

Ser Asp Lys Lys Thr Cys Tyr Glu Met Lys Lys Phe Leu Leu Tyr  
 1565 1570 1575  
 Ala Arg Arg Ser Glu Ile Arg Gly Val Asp Ile Asp Asn Pro Tyr  
 1580 1585 1590  
 Val Asn Phe Ile Thr Ala Phe Thr Val Pro Asp Ile Asp Asp Val  
 1595 1600 1605  
 Ala Val Ile Asp Phe Asp Ala Ser Glu Glu Arg Leu Tyr Trp Thr  
 1610 1615 1620  
 Asp Ile Lys Thr Gln Thr Ile Thr Arg Ala Phe Ile Asn Gly Thr  
 1625 1630 1635  
 Gly Leu Glu Thr Val Ile Ser Arg Asp Ile Gln Ser Ile Arg Gly  
 1640 1645 1650  
 Leu Ala Val Asp Trp Val Ser Arg Asn Leu Tyr Trp Ile Ser Ser  
 1655 1660 1665  
 Glu Phe Asp Glu Thr Gln Ile Asn Val Ala Arg Leu Asp Gly Ser  
 1670 1675 1680  
 Leu Lys Thr Ser Ile Ile His Gly Ile Asp Lys Pro Gln Cys Leu  
 1685 1690 1695  
 Ala Ala His Pro Val Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asn  
 1700 1705 1710  
 Thr Ile Asn Met Ala Asn Met Asp Gly Ser Asn Ser Lys Ile Leu  
 1715 1720 1725  
 Phe Gln Asn Gln Lys Glu Pro Val Gly Leu Ser Ile Asp Tyr Val  
 1730 1735 1740  
 Glu Asn Lys Leu Tyr Trp Ile Ser Ser Gly Asn Gly Thr Ile Asn  
 1745 1750 1755  
 Arg Cys Asn Leu Asp Gly Gly Asn Leu Glu Val Ile Glu Ser Met  
 1760 1765 1770  
 Lys Glu Glu Leu Thr Lys Ala Thr Ala Leu Thr Ile Met Asp Lys  
 1775 1780 1785  
 Lys Leu Trp Trp Ala Asp Gln Asn Leu Ala Gln Leu Gly Thr Cys  
 1790 1795 1800  
 Asn Lys Arg Asp Gly Arg Asn Pro Ser Ile Leu Arg Asn Lys Thr  
 1805 1810 1815

## Nonprovisional IP-017.ST25.txt

Ser Gly Val Val His Met Lys Val Tyr Asp Lys Glu Ala Gln Gln  
 1820 1825 1830  
 Gly Ser Asn Ser Cys Gln Val Asn Asn Gly Gly Cys Ser Gln Leu  
 1835 1840 1845  
 Cys Leu Pro Thr Ser Glu Thr Thr Arg Thr Cys Met Cys Thr Val  
 1850 1855 1860  
 Gly Tyr Tyr Leu Gln Lys Asn Arg Met Ser Cys Gln Gly Ile Glu  
 1865 1870 1875  
 Ser Phe Leu Met Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro  
 1880 1885 1890  
 Leu Glu Pro Arg Asp Lys Val Asp Ala Leu Met Pro Ile Ser Gly  
 1895 1900 1905  
 Ala Ala Phe Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr  
 1910 1915 1920  
 Ile Tyr Trp Thr Asp Met Gly Leu Asn Lys Ile Ser Arg Ala Lys  
 1925 1930 1935  
 Arg Asp Gln Thr Trp Lys Glu Asp Val Val Thr Asn Gly Leu Gly  
 1940 1945 1950  
 Arg Val Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr  
 1955 1960 1965  
 Trp Thr Asp His Gly Phe Asn Leu Ile Glu Val Ala Arg Leu Asn  
 1970 1975 1980  
 Gly Ser Phe Arg Tyr Val Ile Ile Ser Gln Gly Leu Asp Gln Pro  
 1985 1990 1995  
 Arg Ser Ile Ala Val His Pro Glu Lys Gly Phe Leu Phe Trp Thr  
 2000 2005 2010  
 Glu Trp Gly Gln Val Pro Cys Ile Gly Lys Ala Arg Leu Asp Gly  
 2015 2020 2025  
 Ser Glu Lys Val Met Ile Val Ser Val Gly Ile Thr Trp Pro Asn  
 2030 2035 2040  
 Gly Ile Ser Ile Asp Tyr Glu Glu Asn Lys Leu Tyr Trp Cys Asp  
 2045 2050 2055  
 Ala Arg Ser Asp Lys Ile Glu Arg Ile Asp Leu Asp Thr Gly Ala  
 2060 2065 2070

## Nonprovisional IP-017.ST25.txt

Asn	Arg 2075	Glu	Val	Leu	Leu	Ser 2080	Gly	Ser	Asn	Val	Asp 2085	Leu	Phe	Ser
Val	Ala 2090	Val	Phe	Gly	Ala	Tyr 2095	Ile	Tyr	Trp	Ser	Asp 2100	Arg	Ala	His
Ala	Asn 2105	Gly	Ser	Val	Arg	Arg 2110	Gly	His	Lys	Asn	Asp 2115	Ala	Thr	Glu
Thr	Val 2120	Thr	Met	Arg	Thr	Gly 2125	Leu	Gly	Val	Asn	Leu 2130	Lys	Glu	Ile
Lys	Ile 2135	Phe	Asn	Arg	Val	Arg 2140	Glu	Lys	Gly	Thr	Asn 2145	Val	Cys	Ala
Lys	Glu 2150	Asn	Gly	Gly	Cys	Gln 2155	Gln	Leu	Cys	Leu	Tyr 2160	Arg	Gly	Asn
Ser	Arg 2165	Arg	Thr	Cys	Ala	Cys 2170	Ala	His	Gly	Tyr	Leu 2175	Ala	Gly	Asp
Gly	Val 2180	Thr	Cys	Leu	Arg	His 2185	Glu	Gly	Tyr	Leu	Leu 2190	Tyr	Ser	Gly
Arg	Thr 2195	Ile	Leu	Lys	Ser	Ile 2200	His	Leu	Ser	Asp	Glu 2205	Thr	Asn	Leu
Asn	Ser 2210	Pro	Val	Arg	Pro	Tyr 2215	Glu	Asn	Pro	Asn	Tyr 2220	Phe	Lys	Asn
Ile	Ile 2225	Ala	Leu	Ala	Phe	Asp 2230	Tyr	Asn	Gln	Arg	Arg 2235	Glu	Gly	Thr
Asn	Arg 2240	Ile	Phe	Tyr	Ser	Asp 2245	Ala	His	Phe	Gly	Asn 2250	Ile	Gln	Leu
Ile	Lys 2255	Asp	Asn	Trp	Glu	Asp 2260	Arg	Gln	Val	Ile	Val 2265	Glu	Asn	Val
Gly	Ser 2270	Val	Glu	Gly	Leu	Ala 2275	Tyr	His	Arg	Ala	Trp 2280	Asp	Thr	Leu
Tyr	Trp 2285	Thr	Ser	Ser	Ser	Thr 2290	Ser	Ser	Ile	Thr	Arg 2295	His	Thr	Val
Asp	Gln 2300	Thr	Arg	Pro	Gly	Ala 2305	Ile	Asp	Arg	Glu	Ala 2310	Val	Ile	Thr
Met	Ser 2315	Glu	Asp	Asp	His	Pro 2320	His	Val	Leu	Ala	Leu 2325	Asp	Glu	Cys

## Nonprovisional IP-017.ST25.txt

Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Gln His Pro Ser  
 2330 2335 2340  
 Ile Met Arg Ala Thr Leu Thr Gly Lys Asn Ala His Val Val Val  
 2345 2350 2355  
 Ser Thr Asp Ile Leu Thr Pro Asn Gly Leu Thr Ile Asp His Arg  
 2360 2365 2370  
 Ala Glu Lys Leu Tyr Phe Ser Asp Gly Ser Leu Gly Lys Ile Glu  
 2375 2380 2385  
 Arg Cys Glu Tyr Asp Gly Ser Gln Arg His Val Ile Val Lys Ser  
 2390 2395 2400  
 Gly Pro Gly Thr Phe Leu Ser Leu Ala Val Tyr Asp Ser Tyr Ile  
 2405 2410 2415  
 Phe Trp Ser Asp Trp Gly Arg Arg Ala Ile Leu Arg Ser Asn Lys  
 2420 2425 2430  
 Tyr Thr Gly Gly Glu Thr Lys Ile Leu Arg Ser Asp Ile Pro His  
 2435 2440 2445  
 Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys  
 2450 2455 2460  
 Glu Leu Ser Pro Cys Ala Leu Leu Asn Gly Gly Cys His Asp Leu  
 2465 2470 2475  
 Cys Leu Leu Thr Pro Asp Gly Arg Val Asn Cys Ser Cys Arg Gly  
 2480 2485 2490  
 Asp Arg Val Leu Leu Ala Asn Asn Arg Cys Val Thr Lys Asn Ser  
 2495 2500 2505  
 Ser Cys Asn Ile Tyr Ser Glu Phe Glu Cys Gly Asn Gly Asp Cys  
 2510 2515 2520  
 Val Asp Tyr Val Leu Thr Cys Asp Gly Ile Pro His Cys Lys Asp  
 2525 2530 2535  
 Lys Ser Asp Glu Lys Leu Leu Tyr Cys Glu Asn Arg Ser Cys Arg  
 2540 2545 2550  
 Ser Gly Phe Lys Pro Cys Tyr Asn Arg Arg Cys Val Pro His Gly  
 2555 2560 2565  
 Lys Leu Cys Asp Gly Thr Asn Asp Cys Gly Asp Ser Ser Asp Glu  
 2570 2575 2580



## Nonprovisional IP-017.ST25.txt

Leu Asp Cys Lys Val Ser Thr Cys Ser Thr Val Glu Phe Arg Cys  
 2585 2590 2595  
 Ala Asp Gly Thr Cys Ile Pro Arg Ser Ala Arg Cys Asn Gln Asn  
 2600 2605 2610  
 Met Asp Cys Ser Asp Ala Ser Asp Glu Lys Gly Cys Asn Asn Thr  
 2615 2620 2625  
 Asp Cys Thr His Phe Tyr Lys Leu Gly Val Lys Ser Thr Gly Phe  
 2630 2635 2640  
 Ile Arg Cys Asn Ser Thr Ser Leu Cys Val Leu Pro Ser Trp Ile  
 2645 2650 2655  
 Cys Asp Gly Ser Asn Asp Cys Gly Asp Tyr Ser Asp Glu Leu Lys  
 2660 2665 2670  
 Cys Pro Val Gln Asn Lys His Lys Cys Glu Glu Asn Tyr Phe Gly  
 2675 2680 2685  
 Cys Pro Ser Gly Arg Cys Ile Leu Asn Thr Trp Val Cys Asp Gly  
 2690 2695 2700  
 Gln Lys Asp Cys Glu Asp Gly Leu Asp Glu Leu His Cys Asp Ser  
 2705 2710 2715  
 Ser Cys Ser Trp Asn Gln Phe Ala Cys Ser Val Lys Lys Cys Ile  
 2720 2725 2730  
 Ser Lys His Trp Ile Cys Asp Gly Glu Asp Asp Cys Gly Asp Ser  
 2735 2740 2745  
 Leu Asp Glu Ser Asp Ser Ile Cys Gly Ala Val Thr Cys Ala Ala  
 2750 2755 2760  
 Asp Met Phe Ser Cys Gln Gly Ser His Ala Cys Val Pro Gln His  
 2765 2770 2775  
 Trp Leu Cys Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu  
 2780 2785 2790  
 Leu Ser Ser Ala Gly Cys Ala Pro Asn Asn Thr Cys Asp Glu Asn  
 2795 2800 2805  
 Ala Phe Met Cys His Asn Lys Val Cys Ile Pro Lys Gln Phe Val  
 2810 2815 2820  
 Cys Asp His Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu Phe Leu  
 2825 2830 2835

## Nonprovisional IP-017.ST25.txt

Gln Cys Gly Tyr Arg Gln Cys Gly Pro Glu Glu Phe Arg Cys Ala  
 2840 2845 2850  
 Asp Gly Arg Cys Leu Val Asn Thr Leu Trp Gln Cys Asp Gly Asp  
 2855 2860 2865  
 Phe Asp Cys Pro Asp Ser Ser Asp Glu Ala Pro Ile Asn Pro Arg  
 2870 2875 2880  
 Cys Arg Ser Ala Glu His Ser Cys Asn Ser Ser Phe Phe Met Cys  
 2885 2890 2895  
 Lys Asn Gly Arg Cys Ile Pro Ser Asp Gly Leu Cys Asp Ile Arg  
 2900 2905 2910  
 Asp Asp Cys Gly Asp Gly Ser Asp Glu Thr Asn Cys His Ile Asn  
 2915 2920 2925  
 Glu Cys Leu Ser Lys Lys Ile Ser Gly Cys Ser Gln Asp Cys Gln  
 2930 2935 2940  
 Asp Leu Pro Val Ser Tyr Lys Cys Lys Cys Trp Pro Gly Phe Gln  
 2945 2950 2955  
 Leu Lys Asp Asp Gly Lys Thr Cys Val Asp Ile Asp Glu Cys Ser  
 2960 2965 2970  
 Ser Gly Phe Pro Cys Ser Gln Gln Cys Ile Asn Thr Tyr Gly Thr  
 2975 2980 2985  
 Tyr Lys Cys His Cys Ala Glu Gly Tyr Glu Thr Gln Pro Asp Asn  
 2990 2995 3000  
 Pro Asn Gly Cys Arg Ser Leu Ser Asp Glu Glu Pro Phe Leu Ile  
 3005 3010 3015  
 Leu Ala Asp Gln His Glu Ile Arg Lys Ile Ser Thr Asp Gly Ser  
 3020 3025 3030  
 Asn Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Val Ile Ala Leu  
 3035 3040 3045  
 Asp Phe Asp Tyr Arg Glu Glu Phe Ile Tyr Trp Ile Asp Ser Ser  
 3050 3055 3060  
 Arg Pro Asn Gly Ser Arg Ile Asn Arg Met Cys Leu Asn Gly Ser  
 3065 3070 3075  
 Asp Ile Lys Val Val His Asn Thr Ala Val Pro Asn Ala Leu Ala  
 3080 3085 3090

## Nonprovisional IP-017.ST25.txt

Val Asp Trp Ile Gly Lys Asn Leu Tyr Trp Ser Asp Thr Glu Lys  
 3095 3100 3105  
 Arg Ile Ile Glu Val Ser Lys Leu Asn Gly Leu Tyr Pro Thr Val  
 3110 3115 3120  
 Leu Val Ser Lys Arg Leu Lys Phe Pro Arg Asp Leu Ser Leu Asp  
 3125 3130 3135  
 Pro Arg Ala Gly Asn Leu Tyr Trp Ile Asp Cys Cys Glu Tyr Pro  
 3140 3145 3150  
 His Ile Gly Arg Val Gly Met Asp Gly Thr Asn Gln Ser Val Val  
 3155 3160 3165  
 Ile Glu Thr Lys Ile Ser Arg Pro Met Ala Leu Thr Ile Asp Tyr  
 3170 3175 3180  
 Val Asn His Arg Leu Tyr Trp Ala Asp Glu Asn His Ile Glu Phe  
 3185 3190 3195  
 Ser Asn Met Asp Gly Ser His Arg His Lys Val Pro Asn Gln Asp  
 3200 3205 3210  
 Ile Pro Gly Val Ile Ala Leu Thr Leu Phe Glu Asp Tyr Ile Tyr  
 3215 3220 3225  
 Trp Thr Asp Gly Lys Thr Lys Ser Leu Ser Arg Val His Lys Thr  
 3230 3235 3240  
 Ser Gly Ala Asp Arg Leu Ser Leu Ile Asn Ser Trp His Ala Ile  
 3245 3250 3255  
 Thr Asp Ile Gln Val Tyr His Ser Tyr Arg Gln Pro Asp Val Ser  
 3260 3265 3270  
 Lys His Leu Cys Thr Val Asn Asn Gly Gly Cys Ser His Leu Cys  
 3275 3280 3285  
 Leu Leu Gly Pro Gly Lys Thr His Thr Cys Ala Cys Pro Thr Asn  
 3290 3295 3300  
 Phe Tyr Leu Ala Ala Asp Asn Arg Thr Cys Leu Ser Asn Cys Thr  
 3305 3310 3315  
 Ala Ser Gln Phe Arg Cys Lys Thr Asp Lys Cys Ile Pro Phe Trp  
 3320 3325 3330  
 Trp Lys Cys Asp Thr Val Asp Asp Cys Gly Asp Gly Ser Asp Glu  
 3335 3340 3345

## Nonprovisional IP-017.ST25.txt

Pro Asp Asp Cys Pro Glu Phe Lys Cys Gln Pro Gly Arg Phe Gln  
 3350 3355 3360  
 Cys Gly Thr Gly Leu Cys Ala Leu Pro Ala Phe Ile Cys Asp Gly  
 3365 3370 3375  
 Glu Asn Asp Cys Gly Asp Asn Ser Asp Glu Leu Asn Cys Asp Thr  
 3380 3385 3390  
 His Val Cys Leu Ala Gly Gln Phe Lys Cys Thr Lys Asn Lys Lys  
 3395 3400 3405  
 Cys Ile Pro Val Asn Leu Arg Cys Asn Gly Gln Asp Asp Cys Gly  
 3410 3415 3420  
 Asp Glu Glu Asp Glu Lys Asp Cys Pro Glu Asn Ser Cys Ser Pro  
 3425 3430 3435  
 Asp Tyr Phe Gln Cys Lys Thr Thr Lys His Cys Ile Ser Lys Leu  
 3440 3445 3450  
 Trp Val Cys Asp Glu Asp Pro Asp Cys Ala Asp Ala Ser Asp Glu  
 3455 3460 3465  
 Ala Asn Cys Asp Lys Lys Thr Cys Gly Pro His Glu Phe Gln Cys  
 3470 3475 3480  
 Lys Asn Asn Asn Cys Ile Pro Asp His Trp Arg Cys Asp Asn Gln  
 3485 3490 3495  
 Asn Asp Cys Ser Asp Asn Ser Asp Glu Asp Asn Cys Lys Pro Gln  
 3500 3505 3510  
 Thr Cys Thr Leu Lys Asp Phe Leu Cys Ser Asn Gly Asp Cys Val  
 3515 3520 3525  
 Ser Ser Arg Phe Trp Cys Asp Gly Glu Phe Asp Cys Ala Asp Gly  
 3530 3535 3540  
 Ser Asp Glu Lys Asn Cys Glu Thr Ser Cys Ser Lys Asp Gln Phe  
 3545 3550 3555  
 Gln Cys Ser Asn Gly Gln Cys Leu Ser Ala Lys Trp Lys Cys Asp  
 3560 3565 3570  
 Gly His Glu Asp Cys Lys Tyr Gly Glu Asp Glu Lys Asn Cys Glu  
 3575 3580 3585  
 Pro Ala Phe Pro Val Cys Ser Ser Ser Glu Tyr Met Cys Ala Ser  
 3590 3595 3600

## Nonprovisional IP-017.ST25.txt

Gly Gly Cys Leu Ser Ala Ser Leu Lys Cys Asn Gly Glu Pro Asp  
 3605 3610 3615  
 Cys Val Asp Gly Ser Asp Glu Met Asp Cys Val Ile Glu Cys Lys  
 3620 3625 3630  
 Glu Asp Gln Phe Gln Cys Lys Asn Lys Ala Tyr Cys Ile Pro Ile  
 3635 3640 3645  
 Arg Trp Leu Cys Asp Gly Ile Tyr Asp Cys Val Asp Gly Ser Asp  
 3650 3655 3660  
 Glu Glu Thr Cys Gly Arg Gly Ser Ile Cys Arg Asp Asp Glu  
 3665 3670 3675  
 Phe Leu Cys Asn Asn Ser Leu Cys Lys Leu His Phe Trp Val Cys  
 3680 3685 3690  
 Asp Gly Glu Asp Asp Cys Gly Asp Asn Ser Asp Glu Ala Pro Asp  
 3695 3700 3705  
 Met Cys Val Lys Phe Leu Cys Pro Pro Thr Arg Pro Tyr Arg Cys  
 3710 3715 3720  
 Arg Asn Asp Arg Ile Cys Leu Gln Leu Glu Lys Ile Cys Asn Gly  
 3725 3730 3735  
 Ile Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu His Cys Ser Gly  
 3740 3745 3750  
 Lys Leu Ser Leu Lys Ser Lys Pro Cys Lys Lys Asp Glu Phe Thr  
 3755 3760 3765  
 Cys Ser Asn Arg Asn Cys Ile Pro Met Glu Leu Gln Cys Asp Ser  
 3770 3775 3780  
 Leu Asp Asp Cys Gly Asp Gly Ser Asp Glu Gln Gly Cys Leu Lys  
 3785 3790 3795  
 Thr Pro Ile Glu His Thr Cys Glu Asn Asn Gly Asn Pro Cys Gly  
 3800 3805 3810  
 Asp Asp Ala Tyr Cys Asn Gln Ile Lys Thr Ser Val Phe Cys Arg  
 3815 3820 3825  
 Cys Lys Pro Gly Phe Gln Arg Asn Met Lys Gly Arg Glu Cys Ala  
 3830 3835 3840  
 Asp Leu Asn Glu Cys Leu Leu Phe Gly Ile Cys Ser His His Cys  
 3845 3850 3855

## Nonprovisional IP-017.ST25.txt

Leu Asn Thr Arg Gly Ser Tyr Lys Cys Val Cys Asp Gln Asn Phe  
 3860 3865 3870  
 Gln Glu Lys Asn Asn Ser Cys Ile Ala Lys Gly Ser Glu Asp Gln  
 3875 3880 3885  
 Ala Leu Tyr Ile Ala Asn Asp Thr Asp Ile Leu Gly Phe Val Tyr  
 3890 3895 3900  
 Pro Phe Asn Tyr Ser Gly Gly His Gln Gln Ile Ser His Val Glu  
 3905 3910 3915  
 His Asn Ser Arg Ile Thr Gly Met Asp Val His Tyr Gln Arg Asn  
 3920 3925 3930  
 Val Ile Val Trp Ser Thr Gln Phe Asn Pro Gly Gly Ile Phe Tyr  
 3935 3940 3945  
 Lys Met Ile Asp Ala Arg Glu Lys Arg Gln Ala Asn Ser Gly Leu  
 3950 3955 3960  
 Ile Cys Pro Glu Phe Lys Arg Pro Arg Asp Ile Ala Val Asp Trp  
 3965 3970 3975  
 Val Ala Gly Asn Val Tyr Trp Thr Asp His Ser Arg Met His Trp  
 3980 3985 3990  
 Phe Ser Tyr Tyr Thr Thr His Trp Thr Ser Leu Arg Tyr Ser Ile  
 3995 4000 4005  
 Asn Val Gly Gln Leu Asn Gly Pro Asn Cys Thr Arg Leu Leu Thr  
 4010 4015 4020  
 Asn Met Ala Gly Glu Pro Tyr Ala Ile Ala Val Asn Pro Lys Arg  
 4025 4030 4035  
 Gly Met Met Tyr Trp Thr Val Ile Gly Asp His Ser His Ile Glu  
 4040 4045 4050  
 Glu Ala Ala Met Asp Gly Thr Leu Arg Arg Val Leu Val Gln Lys  
 4055 4060 4065  
 Asn Leu Gln Arg Pro Thr Gly Leu Thr Val Asp His Phe Gly Glu  
 4070 4075 4080  
 Arg Ile Tyr Trp Ala Asp Phe Glu Leu Ser Ile Ile Gly Ser Val  
 4085 4090 4095  
 Leu Tyr Asp Gly Ser Ser Pro Val Val Ser Val Ser Ser Lys Gln  
 4100 4105 4110

## Nonprovisional IP-017.ST25.txt

Gly Leu Leu His Pro His Arg Ile Asp Val Phe Glu Asp Tyr Ile  
 4115 4120 4125  
 Tyr Gly Ala Gly Pro Lys Asn Gly Ile Phe Arg Val Gln Lys Phe  
 4130 4135 4140  
 Gly His Gly Ser Val Glu Val Leu Ala Leu Gly Val Asp Lys Thr  
 4145 4150 4155  
 Lys Ser Ile Leu Val Ser His Arg Tyr Lys Gln Leu Asn Leu Pro  
 4160 4165 4170  
 Asn Pro Cys Leu Asp Leu Ser Cys Asp Phe Leu Cys Leu Leu Asn  
 4175 4180 4185  
 Pro Ser Gly Ala Thr Cys Ile Cys Pro Glu Gly Lys Tyr Met Met  
 4190 4195 4200  
 Asn Gly Thr Cys His Asp Asp Ser Leu Leu Asp Asp Ser Cys Lys  
 4205 4210 4215  
 Leu Thr Cys Glu Asn Gly Gly Arg Cys Ile Leu Asn Glu Lys Gly  
 4220 4225 4230  
 Asp Leu Arg Cys His Cys Trp Pro Ser Tyr Ser Gly Gly Arg Cys  
 4235 4240 4245  
 Glu Val Asn His Cys Ser Asn Tyr Cys Gln Asn Gly Gly Thr Cys  
 4250 4255 4260  
 Ile Pro Ser Thr Leu Gly Arg Pro Thr Cys Ile Cys Ala Leu Gly  
 4265 4270 4275  
 Phe Thr Gly Pro Asn Cys Gly Lys Ala Val Cys Glu Asp Ser Cys  
 4280 4285 4290  
 His Asn Gly Gly Ser Cys Val Val Thr Ala Gly Asn Gln Pro Tyr  
 4295 4300 4305  
 Cys His Cys Gln Ala Asp Tyr Thr Gly Asp Arg Cys Gln Tyr Tyr  
 4310 4315 4320  
 Val Cys His His Tyr Cys Val Asn Ser Glu Ser Cys Thr Ile Gly  
 4325 4330 4335  
 Asn Asp Gly Ser Val Glu Cys Val Cys Pro Thr Arg Tyr Glu Gly  
 4340 4345 4350  
 Pro Lys Cys Glu Ile Asp Lys Cys Val Arg Cys His Gly Gly His  
 4355 4360 4365

## Nonprovisional IP-017.ST25.txt

Cys Ile Ile Asn Lys Asp Asn Glu Asp Ile Phe Cys Asn Cys Thr  
 4370 4375 4380  
 Asn Gly Lys Ile Ala Ser Ser Cys Gln Leu Cys Asp Gly Tyr Cys  
 4385 4390 4395  
 Tyr Asn Gly Gly Thr Cys Gln Leu Asp Pro Glu Thr Ser Ile Pro  
 4400 4405 4410  
 Val Cys Val Cys Ser Thr Asn Trp Ser Gly Thr Gln Cys Glu Arg  
 4415 4420 4425  
 Pro Ala Pro Lys Ser Ser Lys Ser Glu His Ile Ser Thr Arg Ser  
 4430 4435 4440  
 Ile Ala Ile Ile Val Pro Leu Val Leu Leu Val Thr Leu Val Thr  
 4445 4450 4455  
 Thr Leu Val Ile Gly Leu Val Val Cys Lys Arg Lys Arg Arg Thr  
 4460 4465 4470  
 Lys Thr Ile Arg Arg Gln Pro Ile Ile Asn Gly Gly Ile Asn Val  
 4475 4480 4485  
 Glu Ile Gly Asn Pro Ser Tyr Asn Met Tyr Glu Val Asp His Asp  
 4490 4495 4500  
 His Ser Asp Gly Gly Leu Leu Glu Pro Ser Phe Met Ile Asp Pro  
 4505 4510 4515  
 Val Lys Ser Arg Tyr Ile Gly Gly Gly Ser Ser Ala Phe Lys Leu  
 4520 4525 4530  
 Pro His Thr Ala Pro Pro Ile Tyr Leu Asn Ser Asp Leu Lys Gly  
 4535 4540 4545  
 Pro Leu Thr Phe Gly Pro Thr Asn Tyr Ser Asn Pro Val Tyr Ala  
 4550 4555 4560  
 Lys Leu Tyr Met Asp Gly Gln Asn Cys Arg Asn Ser Leu Ala Ser  
 4565 4570 4575  
 Val Asp Glu Arg Lys Glu Leu Leu Pro Lys Lys Ile Glu Ile Gly  
 4580 4585 4590  
 Ile Arg Glu Thr Val Ala  
 4595

<210> 71  
 <211> 4545  
 <212> PRT



## Nonprovisional IP-017.ST25.txt

&lt;213&gt; MOUSE

&lt;400&gt; 71

Met Leu Thr Pro Pro Leu Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu  
 1 5 10 15

Val Ser Gly Ala Thr Met Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln  
 20 25 30

Phe Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys  
 35 40 45

Asp Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile  
 50 55 60

Cys Pro Gln Ser Lys Ala Gln Arg Cys Pro Pro Asn Glu His Ser Cys  
 65 70 75 80

Leu Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Ile  
 85 90 95

Gln Asp Cys Met Asp Gly Ser Asp Glu Gly Ala His Cys Arg Glu Leu  
 100 105 110

Arg Ala Asn Cys Ser Arg Met Gly Cys Gln His His Cys Val Pro Thr  
 115 120 125

Pro Ser Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala  
 130 135 140

Asp Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr  
 145 150 155 160

Cys Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Thr Cys Gly Cys  
 165 170 175

Val Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys  
 180 185 190

Asn Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln  
 195 200 205

Asn Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr  
 210 215 220

Pro Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn  
 225 230 235 240

Glu Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln  
 245 250 255

## Nonprovisional IP-017.ST25.txt

Leu Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His  
 260 265 270

Thr Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile  
 275 280 285

Asp Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg  
 290 295 300

Ile Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp  
 305 310 315 320

Leu Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly  
 325 330 335

Lys Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys  
 340 345 350

Asp Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val  
 355 360 365

Phe Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp  
 370 375 380

Ala Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys  
 385 390 395 400

Gly Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly  
 405 410 415

Leu Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala  
 420 425 430

Asn Thr Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser  
 435 440 445

Thr Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His  
 450 455 460

Ile Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu  
 465 470 475 480

Asn Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu  
 485 490 495

Ala Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser  
 500 505 510

Leu Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe  
 515 520 525

## Nonprovisional IP-017.ST25.txt

Leu Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met  
 530 535 540

Gly Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met  
 545 550 555 560

Asn Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe  
 565 570 575

Ala Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr  
 580 585 590

Glu Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val  
 595 600 605

Ala Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro  
 610 615 620

Lys Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg  
 625 630 635 640

Lys Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val  
 645 650 655

Asp Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro  
 660 665 670

Lys Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser  
 675 680 685

His Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly  
 690 695 700

Leu Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe  
 705 710 715 720

Tyr Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile  
 725 730 735

Val Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His  
 740 745 750

Gly Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg  
 755 760 765

Leu Glu Arg Gly Val Ala Gly Ala Pro Pro Thr Val Thr Leu Leu Arg  
 770 775 780

Ser Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln  
 785 790 795 800

Nonprovisional IP-017.ST25.txt

Gln Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser  
 805 810 815  
 Ser Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu  
 820 825 830  
 Asp Gln Val Leu Asp Thr Asp Gly Val Thr Cys Leu Ala Asn Pro Ser  
 835 840 845  
 Tyr Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn  
 850 855 860  
 Asn Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys  
 865 870 875 880  
 Leu Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys  
 885 890 895  
 Pro Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg  
 900 905 910  
 Trp Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser  
 915 920 925  
 Asn Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys  
 930 935 940  
 Ala Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp  
 945 950 955 960  
 Asp Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr  
 965 970 975  
 Cys Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn  
 980 985 990  
 Ile Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp  
 995 1000 1005  
 Glu Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys  
 1010 1015 1020  
 Asn Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp  
 1025 1030 1035  
 Asn Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr  
 1040 1045 1050  
 Asn Gln Ala Thr Arg Pro Pro Gly Gly Cys His Ser Asp Glu Phe  
 1055 1060 1065

## Nonprovisional IP-017.ST25.txt

Gln Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys  
 1070 1075 1080  
 Asp Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys  
 1085 1090 1095  
 Glu Gly Val Thr His Val Cys Asp Pro Asn Val Lys Phe Gly Cys  
 1100 1105 1110  
 Lys Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly  
 1115 1120 1125  
 Asp Ser Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ala  
 1130 1135 1140  
 Leu Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser  
 1145 1150 1155  
 Val Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Lys Asp Asp Cys  
 1160 1165 1170  
 Gly Asp Gly Ser Asp Glu Gly Glu Leu Cys Asp Gln Cys Ser Leu  
 1175 1180 1185  
 Asn Asn Gly Gly Cys Ser His Asn Cys Ser Val Ala Pro Gly Glu  
 1190 1195 1200  
 Gly Ile Val Cys Ser Cys Pro Leu Gly Met Glu Leu Gly Ser Asp  
 1205 1210 1215  
 Asn His Thr Cys Gln Ile Gln Ser Tyr Cys Ala Lys His Leu Lys  
 1220 1225 1230  
 Cys Ser Gln Lys Cys Asp Gln Asn Lys Phe Ser Val Lys Cys Ser  
 1235 1240 1245  
 Cys Tyr Glu Gly Trp Val Leu Glu Pro Asp Gly Glu Ser Cys Arg  
 1250 1255 1260  
 Ser Leu Asp Pro Phe Lys Pro Phe Ile Ile Phe Ser Asn Arg His  
 1265 1270 1275  
 Glu Ile Arg Arg Ile Asp Leu His Lys Gly Asp Tyr Ser Val Leu  
 1280 1285 1290  
 Val Pro Gly Leu Arg Asn Thr Ile Ala Leu Asp Phe His Leu Ser  
 1295 1300 1305  
 Gln Ser Ala Leu Tyr Trp Thr Asp Val Val Glu Asp Lys Ile Tyr  
 1310 1315 1320

## Nonprovisional IP-017.ST25.txt

Arg Gly Lys Leu Leu Asp Asn Gly Ala Leu Thr Ser Phe Glu Val  
 1325 1330 1335  
 Val Ile Gln Tyr Gly Leu Ala Thr Pro Glu Gly Leu Ala Val Asp  
 1340 1345 1350  
 Trp Ile Ala Gly Asn Ile Tyr Trp Val Glu Ser Asn Leu Asp Gln  
 1355 1360 1365  
 Ile Glu Val Ala Lys Leu Asp Gly Thr Leu Arg Thr Thr Leu Leu  
 1370 1375 1380  
 Ala Gly Asp Ile Glu His Pro Arg Ala Ile Ala Leu Asp Pro Arg  
 1385 1390 1395  
 Asp Gly Ile Leu Phe Trp Thr Asp Trp Asp Ala Ser Leu Pro Arg  
 1400 1405 1410  
 Ile Glu Ala Ala Ser Met Ser Gly Ala Gly Arg Arg Thr Ile His  
 1415 1420 1425  
 Arg Glu Thr Gly Ser Gly Gly Trp Pro Asn Gly Leu Thr Val Asp  
 1430 1435 1440  
 Tyr Leu Glu Lys Arg Ile Leu Trp Ile Asp Ala Arg Ser Asp Ala  
 1445 1450 1455  
 Ile Tyr Ser Ala Arg Tyr Asp Gly Ser Gly His Met Glu Val Leu  
 1460 1465 1470  
 Arg Gly His Glu Phe Leu Ser His Pro Phe Ala Val Thr Leu Tyr  
 1475 1480 1485  
 Gly Gly Glu Val Tyr Trp Thr Asp Trp Arg Thr Asn Thr Leu Ala  
 1490 1495 1500  
 Lys Ala Asn Lys Trp Thr Gly His Asn Val Thr Val Val Gln Arg  
 1505 1510 1515  
 Thr Asn Thr Gln Pro Phe Asp Leu Gln Val Tyr His Pro Ser Arg  
 1520 1525 1530  
 Gln Pro Met Ala Pro Asn Pro Cys Glu Ala Asn Gly Gly Arg Gly  
 1535 1540 1545  
 Pro Cys Ser His Leu Cys Leu Ile Asn Tyr Asn Arg Thr Val Ser  
 1550 1555 1560  
 Cys Ala Cys Pro His Leu Met Lys Leu His Lys Asp Asn Thr Thr  
 1565 1570 1575

## Nonprovisional IP-017.ST25.txt

Cys Tyr Glu Phe Lys Lys Phe Leu Leu Tyr Ala Arg Gln Met Glu  
 1580 1585 1590  
 Ile Arg Gly Val Asp Leu Asp Ala Pro Tyr Tyr Asn Tyr Ile Ile  
 1595 1600 1605  
 Ser Phe Thr Val Pro Asp Ile Asp Asn Val Thr Val Leu Asp Tyr  
 1610 1615 1620  
 Asp Ala Arg Glu Gln Arg Val Tyr Trp Ser Asp Val Arg Thr Gln  
 1625 1630 1635  
 Ala Ile Lys Arg Ala Phe Ile Asn Gly Thr Gly Val Glu Thr Val  
 1640 1645 1650  
 Val Ser Ala Asp Leu Pro Asn Ala His Gly Leu Ala Val Asp Trp  
 1655 1660 1665  
 Val Ser Arg Asn Leu Phe Trp Thr Ser Tyr Asp Thr Asn Lys Lys  
 1670 1675 1680  
 Gln Ile Asn Val Ala Arg Leu Asp Gly Ser Phe Lys Asn Ala Val  
 1685 1690 1695  
 Val Gln Gly Leu Glu Gln Pro His Gly Leu Val Val His Pro Leu  
 1700 1705 1710  
 Arg Gly Lys Leu Tyr Trp Thr Asp Gly Asp Asn Ile Ser Met Ala  
 1715 1720 1725  
 Asn Met Asp Gly Ser Asn His Thr Leu Leu Phe Ser Gly Gln Lys  
 1730 1735 1740  
 Gly Pro Val Gly Leu Ala Ile Asp Phe Pro Glu Ser Lys Leu Tyr  
 1745 1750 1755  
 Trp Ile Ser Ser Gly Asn His Thr Ile Asn Arg Cys Asn Leu Asp  
 1760 1765 1770  
 Gly Ser Glu Leu Glu Val Ile Asp Thr Met Arg Ser Gln Leu Gly  
 1775 1780 1785  
 Lys Ala Thr Ala Leu Ala Ile Met Gly Asp Lys Leu Trp Trp Ala  
 1790 1795 1800  
 Asp Gln Val Ser Glu Lys Met Gly Thr Cys Asn Lys Ala Asp Gly  
 1805 1810 1815  
 Ser Gly Ser Val Val Leu Arg Asn Ser Thr Thr Leu Val Met His  
 1820 1825 1830

## Nonprovisional IP-017.ST25.txt

Met Lys Val Tyr Asp Glu Ser Ile Gln Leu Glu His Glu Gly Thr  
 1835 1840 1845  
 Asn Pro Cys Ser Val Asn Asn Gly Asp Cys Ser Gln Leu Cys Leu  
 1850 1855 1860  
 Pro Thr Ser Glu Thr Thr Arg Ser Cys Met Cys Thr Ala Gly Tyr  
 1865 1870 1875  
 Ser Leu Arg Ser Gly Gln Gln Ala Cys Glu Gly Val Gly Ser Phe  
 1880 1885 1890  
 Leu Leu Tyr Ser Val His Glu Gly Ile Arg Gly Ile Pro Leu Asp  
 1895 1900 1905  
 Pro Asn Asp Lys Ser Asp Ala Leu Val Pro Val Ser Gly Thr Ser  
 1910 1915 1920  
 Leu Ala Val Gly Ile Asp Phe His Ala Glu Asn Asp Thr Ile Tyr  
 1925 1930 1935  
 Trp Val Asp Met Gly Leu Ser Thr Ile Ser Arg Ala Lys Arg Asp  
 1940 1945 1950  
 Gln Thr Trp Arg Glu Asp Val Val Thr Asn Gly Ile Gly Arg Val  
 1955 1960 1965  
 Glu Gly Ile Ala Val Asp Trp Ile Ala Gly Asn Ile Tyr Trp Thr  
 1970 1975 1980  
 Asp Gln Gly Phe Asp Val Ile Glu Val Ala Arg Leu Asn Gly Ser  
 1985 1990 1995  
 Phe Arg Tyr Val Val Ile Ser Gln Gly Leu Asp Lys Pro Arg Ala  
 2000 2005 2010  
 Ile Thr Val His Pro Glu Lys Gly Tyr Leu Phe Trp Thr Glu Trp  
 2015 2020 2025  
 Gly His Tyr Pro Arg Ile Glu Arg Ser Arg Leu Asp Gly Thr Glu  
 2030 2035 2040  
 Arg Val Val Leu Val Asn Val Ser Ile Ser Trp Pro Asn Gly Ile  
 2045 2050 2055  
 Ser Val Asp Tyr Gln Gly Gly Lys Leu Tyr Trp Cys Asp Ala Arg  
 2060 2065 2070  
 Met Asp Lys Ile Glu Arg Ile Asp Leu Glu Thr Gly Glu Asn Arg  
 2075 2080 2085



## Nonprovisional IP-017.ST25.txt

Glu Val Val Leu Ser Ser Asn Asn Met Asp Met Phe Ser Val Ser  
 2090 2095 2100  
 Val Phe Glu Asp Phe Ile Tyr Trp Ser Asp Arg Thr His Ala Asn  
 2105 2110 2115  
 Gly Ser Ile Lys Arg Gly Cys Lys Asp Asn Ala Thr Asp Ser Val  
 2120 2125 2130  
 Pro Leu Arg Thr Gly Ile Gly Val Gln Leu Lys Asp Ile Lys Val  
 2135 2140 2145  
 Phe Asn Arg Asp Arg Gln Lys Gly Thr Asn Val Cys Ala Val Ala  
 2150 2155 2160  
 Asn Gly Gly Cys Gln Gln Leu Cys Leu Tyr Arg Gly Gly Gly Gln  
 2165 2170 2175  
 Arg Ala Cys Ala Cys Ala His Gly Met Leu Ala Glu Asp Gly Ala  
 2180 2185 2190  
 Ser Cys Arg Glu Tyr Ala Gly Tyr Leu Leu Tyr Ser Glu Arg Thr  
 2195 2200 2205  
 Ile Leu Lys Ser Ile His Leu Ser Asp Glu Arg Asn Leu Asn Ala  
 2210 2215 2220  
 Pro Val Gln Pro Phe Glu Asp Pro Glu His Met Lys Asn Val Ile  
 2225 2230 2235  
 Ala Leu Ala Phe Asp Tyr Arg Ala Gly Thr Ser Pro Gly Thr Pro  
 2240 2245 2250  
 Asn Arg Ile Phe Phe Ser Asp Ile His Phe Gly Asn Ile Gln Gln  
 2255 2260 2265  
 Ile Asn Asp Asp Gly Ser Gly Arg Thr Thr Ile Val Glu Asn Val  
 2270 2275 2280  
 Gly Ser Val Glu Gly Leu Ala Tyr His Arg Gly Trp Asp Thr Leu  
 2285 2290 2295  
 Tyr Trp Thr Ser Tyr Thr Thr Ser Thr Ile Thr Arg His Thr Val  
 2300 2305 2310  
 Asp Gln Thr Arg Pro Gly Ala Phe Glu Arg Glu Thr Val Ile Thr  
 2315 2320 2325  
 Met Ser Gly Asp Asp His Pro Arg Ala Phe Val Leu Asp Glu Cys  
 2330 2335 2340

## Nonprovisional IP-017.ST25.txt

Gln Asn Leu Met Phe Trp Thr Asn Trp Asn Glu Leu His Pro Ser  
 2345 2350 2355  
 Ile Met Arg Ala Ala Leu Ser Gly Ala Asn Val Leu Thr Leu Ile  
 2360 2365 2370  
 Glu Lys Asp Ile Arg Thr Pro Asn Gly Leu Ala Ile Asp His Arg  
 2375 2380 2385  
 Ala Glu Lys Leu Tyr Phe Ser Asp Ala Thr Leu Asp Lys Ile Glu  
 2390 2395 2400  
 Arg Cys Glu Tyr Asp Gly Ser His Arg Tyr Val Ile Leu Lys Ser  
 2405 2410 2415  
 Glu Pro Val His Pro Phe Gly Leu Ala Val Tyr Gly Glu His Ile  
 2420 2425 2430  
 Phe Trp Thr Asp Trp Val Arg Arg Ala Val Gln Arg Ala Asn Lys  
 2435 2440 2445  
 Tyr Val Gly Ser Asp Met Lys Leu Leu Arg Val Asp Ile Pro Gln  
 2450 2455 2460  
 Gln Pro Met Gly Ile Ile Ala Val Ala Asn Asp Thr Asn Ser Cys  
 2465 2470 2475  
 Glu Leu Ser Pro Cys Arg Ile Asn Asn Gly Gly Cys Gln Asp Leu  
 2480 2485 2490  
 Cys Leu Leu Thr His Gln Gly His Val Asn Cys Ser Cys Arg Gly  
 2495 2500 2505  
 Gly Arg Ile Leu Gln Glu Asp Phe Thr Cys Arg Ala Val Asn Ser  
 2510 2515 2520  
 Ser Cys Arg Ala Gln Asp Glu Phe Glu Cys Ala Asn Gly Glu Cys  
 2525 2530 2535  
 Ile Ser Phe Ser Leu Thr Cys Asp Gly Val Ser His Cys Lys Asp  
 2540 2545 2550  
 Lys Ser Asp Glu Lys Pro Ser Tyr Cys Asn Ser Arg Arg Cys Lys  
 2555 2560 2565  
 Lys Thr Phe Arg Gln Cys Asn Asn Gly Arg Cys Val Ser Asn Met  
 2570 2575 2580  
 Leu Trp Cys Asn Gly Val Asp Asp Cys Gly Asp Gly Ser Asp Glu  
 2585 2590 2595

Nonprovisional IP-017.ST25.txt

Ile Pro Cys Asn Lys Thr Ala Cys Gly Val Gly Glu Phe Arg Cys  
 2600 2605 2610  
 Arg Asp Gly Ser Cys Ile Gly Asn Ser Ser Arg Cys Asn Gln Phe  
 2615 2620 2625  
 Val Asp Cys Glu Asp Ala Ser Asp Glu Met Asn Cys Ser Ala Thr  
 2630 2635 2640  
 Asp Cys Ser Ser Tyr Phe Arg Leu Gly Val Lys Gly Val Leu Phe  
 2645 2650 2655  
 Gln Pro Cys Glu Arg Thr Ser Leu Cys Tyr Ala Pro Ser Trp Val  
 2660 2665 2670  
 Cys Asp Gly Ala Asn Asp Cys Gly Asp Tyr Ser Asp Glu Arg Asp  
 2675 2680 2685  
 Cys Pro Gly Val Lys Arg Pro Arg Cys Pro Leu Asn Tyr Phe Ala  
 2690 2695 2700  
 Cys Pro Ser Gly Arg Cys Ile Pro Met Ser Trp Thr Cys Asp Lys  
 2705 2710 2715  
 Glu Asp Asp Cys Glu Asn Gly Glu Asp Glu Thr His Cys Asn Lys  
 2720 2725 2730  
 Phe Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile  
 2735 2740 2745  
 Ser Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly  
 2750 2755 2760  
 Ser Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser  
 2765 2770 2775  
 Ser Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp  
 2780 2785 2790  
 Leu Cys Asp Gly Asp Lys Asp Cys Thr Asp Gly Ala Asp Glu Ser  
 2795 2800 2805  
 Val Thr Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu  
 2810 2815 2820  
 Phe Met Cys Gln Asn Arg Leu Cys Ile Pro Lys His Phe Val Cys  
 2825 2830 2835  
 Asp His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu  
 2840 2845 2850

## Nonprovisional IP-017.ST25.txt

Cys Glu Tyr Pro Thr Cys Gly Pro Asn Glu Phe Arg Cys Ala Asn  
 2855 2860 2865  
 Gly Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn  
 2870 2875 2880  
 Asp Cys His Asp His Ser Asp Glu Ala Pro Lys Asn Pro His Cys  
 2885 2890 2895  
 Thr Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys  
 2900 2905 2910  
 Ser Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln  
 2915 2920 2925  
 Asp Asp Cys Gly Asp Gly Ser Asp Glu Arg Gly Cys His Val Asn  
 2930 2935 2940  
 Glu Cys Leu Ser Arg Lys Leu Ser Gly Cys Ser Gln Asp Cys Glu  
 2945 2950 2955  
 Asp Leu Lys Ile Gly Phe Lys Cys Arg Cys Arg Pro Gly Phe Arg  
 2960 2965 2970  
 Leu Lys Asp Asp Gly Arg Thr Cys Ala Asp Leu Asp Glu Cys Ser  
 2975 2980 2985  
 Thr Thr Phe Pro Cys Ser Gln Leu Cys Ile Asn Thr His Gly Ser  
 2990 2995 3000  
 Tyr Lys Cys Leu Cys Val Glu Gly Tyr Ala Pro Arg Gly Gly Asp  
 3005 3010 3015  
 Pro His Ser Cys Lys Ala Val Thr Asp Glu Glu Pro Phe Leu Ile  
 3020 3025 3030  
 Phe Ala Asn Arg Tyr Tyr Leu Arg Lys Leu Asn Leu Asp Gly Ser  
 3035 3040 3045  
 Asn Tyr Thr Leu Leu Lys Gln Gly Leu Asn Asn Ala Val Ala Leu  
 3050 3055 3060  
 Asp Phe Asp Tyr Arg Glu Gln Met Ile Tyr Trp Thr Asp Val Thr  
 3065 3070 3075  
 Thr Gln Gly Ser Met Ile Arg Arg Met His Leu Asn Gly Ser Asn  
 3080 3085 3090  
 Val Gln Val Leu His Arg Thr Gly Leu Ser Asn Pro Asp Gly Leu  
 3095 3100 3105

Nonprovisional IP-017.ST25.txt

Ala Val Asp Trp Val Gly Gly Asn Leu Tyr Trp Cys Asp Lys Gly  
 3110 3115 3120  
 Arg Asp Thr Ile Glu Val Ser Lys Leu Asn Gly Ala Tyr Arg Thr  
 3125 3130 3135  
 Val Leu Val Ser Ser Gly Leu Arg Glu Pro Arg Ala Leu Val Val  
 3140 3145 3150  
 Asp Val Gln Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His  
 3155 3160 3165  
 Ser Leu Ile Gly Arg Ile Gly Met Asp Gly Ser Gly Arg Ser Ile  
 3170 3175 3180  
 Ile Val Asp Thr Lys Ile Thr Trp Pro Asn Gly Leu Thr Val Asp  
 3185 3190 3195  
 Tyr Val Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr  
 3200 3205 3210  
 Ile Glu Phe Ala Ser Leu Asp Gly Ser Asn Arg His Val Val Leu  
 3215 3220 3225  
 Ser Gln Asp Ile Pro His Ile Phe Ala Leu Thr Leu Phe Glu Asp  
 3230 3235 3240  
 Tyr Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala  
 3245 3250 3255  
 His Lys Thr Thr Gly Ala Asn Lys Thr Leu Leu Ile Ser Thr Leu  
 3260 3265 3270  
 His Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro  
 3275 3280 3285  
 Asp Val Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser  
 3290 3295 3300  
 Asn Leu Cys Leu Leu Ser Pro Gly Gly Gly His Lys Cys Ala Cys  
 3305 3310 3315  
 Pro Thr Asn Phe Tyr Leu Gly Gly Asp Gly Arg Thr Cys Val Ser  
 3320 3325 3330  
 Asn Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile  
 3335 3340 3345  
 Pro Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His  
 3350 3355 3360

## Nonprovisional IP-017.ST25.txt

Ser Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro Gly  
 3365 3370 3375  
 Gln Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe Ile  
 3380 3385 3390  
 Cys Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn  
 3395 3400 3405  
 Cys Asp Ile His Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn  
 3410 3415 3420  
 Thr Asn Arg Cys Ile Pro Gly Ile Phe Arg Cys Asn Gly Gln Asp  
 3425 3430 3435  
 Asn Cys Gly Asp Gly Glu Asp Glu Arg Asp Cys Pro Glu Val Thr  
 3440 3445 3450  
 Cys Ala Pro Asn Gln Phe Gln Cys Ser Ile Thr Lys Arg Cys Ile  
 3455 3460 3465  
 Pro Arg Val Trp Val Cys Asp Arg Asp Asn Asp Cys Val Asp Gly  
 3470 3475 3480  
 Ser Asp Glu Pro Ala Asn Cys Thr Gln Met Thr Cys Gly Val Asp  
 3485 3490 3495  
 Glu Phe Arg Cys Lys Asp Ser Gly Arg Cys Ile Pro Ala Arg Trp  
 3500 3505  
 Lys Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp Glu Pro  
 3515 3520 3525  
 Lys Glu Glu Cys Asp Glu Arg Thr Cys Glu Pro Tyr Gln Phe Arg  
 3530 3535 3540  
 Cys Lys Asn Asn Arg Cys Val Pro Gly Arg Trp Gln Cys Asp Tyr  
 3545 3550 3555  
 Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu Ser Cys Thr Pro  
 3560 3565 3570  
 Arg Pro Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn Gly Arg Cys  
 3575 3580 3585  
 Ile Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp Cys Ala Asp  
 3590 3595 3600  
 Gly Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met Asp Gln  
 3605 3610 3615

## Nonprovisional IP-017.ST25.txt

Phe Gln Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Arg Cys  
 3620 3625 3630  
 Asp Ala Asp Ala Asp Cys Met Asp Gly Ser Asp Glu Glu Ala Cys  
 3635 3640 3645  
 Gly Thr Gly Val Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn  
 3650 3655 3660  
 Asn Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp  
 3665 3670 3675  
 Asp Cys Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg  
 3680 3685 3690  
 Phe Ile Cys Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg  
 3695 3700 3705  
 Val Cys Leu Trp Ile Gly Arg Gln Cys Asp Gly Val Asp Asn Cys  
 3710 3715 3720  
 Gly Asp Gly Thr Asp Glu Glu Asp Cys Glu Pro Pro Thr Ala Gln  
 3725 3730 3735  
 Asn Pro His Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln  
 3740 3745 3750  
 Arg Cys Leu Ser Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys  
 3755 3760 3765  
 Gly Asp Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp Pro Lys Leu  
 3770 3775 3780  
 Thr Ser Cys Ala Thr Asn Ala Ser Met Cys Gly Asp Glu Ala Arg  
 3785 3790 3795  
 Cys Val Arg Thr Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser Gly  
 3800 3805 3810  
 Phe His Thr Val Pro Gly Gln Pro Gly Cys Gln Asp Ile Asn Glu  
 3815 3820 3825  
 Cys Leu Arg Phe Gly Thr Cys Ser Gln Leu Cys Asn Asn Thr Lys  
 3830 3835 3840  
 Gly Gly His Leu Cys Ser Cys Ala Arg Asn Phe Met Lys Thr His  
 3845 3850 3855  
 Asn Thr Cys Lys Ala Glu Gly Ser Glu Tyr Gln Val Leu Tyr Ile  
 3860 3865 3870

## Nonprovisional IP-017.ST25.txt

Ala Asp Asp Asn Glu Ile Arg Ser Leu Phe Pro Gly His Pro His  
 3875 3880 3885  
 Ser Ala Tyr Glu Gln Thr Phe Gln Gly Asp Glu Ser Val Arg Ile  
 3890 3895 3900  
 Asp Ala Met Asp Val His Val Lys Ala Gly Arg Val Tyr Trp Thr  
 3905 3910 3915  
 Asn Trp His Thr Gly Thr Ile Ser Tyr Arg Ser Leu Pro Pro Ala  
 3920 3925 3930  
 Ala Pro Pro Thr Thr Ser Asn Arg His Arg Arg Gln Ile Asp Arg  
 3935 3940 3945  
 Gly Val Thr His Leu Asn Ile Ser Gly Leu Lys Met Pro Arg Gly  
 3950 3955 3960  
 Ile Ala Ile Asp Trp Val Ala Gly Asn Val Tyr Trp Thr Asp Ser  
 3965 3970 3975  
 Gly Arg Asp Val Ile Glu Val Ala Gln Met Lys Gly Glu Asn Arg  
 3980 3985 3990  
 Lys Thr Leu Ile Ser Gly Met Ile Asp Glu Pro His Ala Ile Val  
 3995 4000 4005  
 Val Asp Pro Leu Arg Gly Thr Met Tyr Trp Ser Asp Trp Gly Asn  
 4010 4015 4020  
 His Pro Lys Ile Glu Thr Ala Ala Met Asp Gly Thr Leu Arg Glu  
 4025 4030 4035  
 Thr Leu Val Gln Asp Asn Ile Gln Trp Pro Thr Gly Leu Ala Val  
 4040 4045 4050  
 Asp Tyr His Asn Glu Arg Leu Tyr Trp Ala Asp Ala Lys Leu Ser  
 4055 4060 4065  
 Val Ile Gly Ser Ile Arg Leu Asn Gly Thr Asp Pro Ile Val Ala  
 4070 4075 4080  
 Ala Asp Ser Lys Arg Gly Leu Ser His Pro Phe Ser Ile Asp Val  
 4085 4090 4095  
 Phe Glu Asp Tyr Ile Tyr Gly Val Thr Tyr Ile Asn Asn Arg Val  
 4100 4105 4110  
 Phe Lys Ile His Lys Phe Gly His Ser Pro Leu Ile Asn Leu Thr  
 4115 4120 4125



Nonprovisional IP-017.ST25.txt

Gly Gly Leu Ser His Ala Ser Asp Val Val Leu Tyr His Gln His  
 4130 4135 4140  
 Lys Gln Pro Glu Val Thr Asn Pro Cys Asp Arg Lys Lys Cys Glu  
 4145 4150 4155  
 Trp Leu Cys Leu Leu Ser Pro Ser Gly Pro Val Cys Thr Cys Pro  
 4160 4165 4170  
 Asn Gly Lys Arg Leu Asp Asn Gly Thr Cys Val Pro Val Pro Ser  
 4175 4180 4185  
 Pro Thr Pro Pro Pro Asp Ala Pro Arg Pro Gly Thr Cys Thr Leu  
 4190 4195 4200  
 Gln Cys Phe Asn Gly Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln  
 4205 4210 4215  
 Pro Lys Cys Arg Cys Gln Pro Arg Tyr Thr Gly Asp Lys Cys Glu  
 4220 4225 4230  
 Leu Asp Gln Cys Trp Glu Tyr Cys His Asn Gly Gly Thr Cys Ala  
 4235 4240 4245  
 Ala Ser Pro Ser Gly Met Pro Thr Cys Arg Cys Pro Thr Gly Phe  
 4250 4255 4260  
 Thr Gly Pro Lys Cys Thr Ala Gln Val Cys Ala Gly Tyr Cys Ser  
 4265 4270 4275  
 Asn Asn Ser Thr Cys Thr Val Asn Gln Gly Asn Gln Pro Gln Cys  
 4280 4285 4290  
 Arg Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys Gln Tyr Arg Gln  
 4295 4300 4305  
 Cys Ser Gly Phe Cys Glu Asn Phe Gly Thr Cys Gln Met Ala Ala  
 4310 4315 4320  
 Asp Gly Ser Arg Gln Cys Arg Cys Thr Val Tyr Phe Glu Gly Pro  
 4325 4330 4335  
 Arg Cys Glu Val Asn Lys Cys Ser Arg Cys Leu Gln Gly Ala Cys  
 4340 4345 4350  
 Val Val Asn Lys Gln Thr Gly Asp Val Thr Cys Asn Cys Thr Asp  
 4355 4360 4365  
 Gly Arg Val Ala Pro Ser Cys Leu Thr Cys Ile Asp His Cys Ser  
 4370 4375 4380

Nonprovisional IP-017.ST25.txt

Asn Gly Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys  
 4385 4390 4395

Gln Cys Pro Pro His Met Thr Gly Pro Arg Cys Glu Glu Gln Val  
 4400 4405 4410

Val Ser Gln Gln Gln Pro Gly His Met Ala Ser Ile Leu Ile Pro  
 4415 4420 4425

Leu Leu Leu Leu Leu Leu Leu Leu Val Ala Gly Val Val Phe  
 4430 4435 4440

Trp Tyr Lys Arg Arg Val Arg Gly Ala Lys Gly Phe Gln His Gln  
 4445 4450 4455

Arg Met Thr Asn Gly Ala Met Asn Val Glu Ile Gly Asn Pro Thr  
 4460 4465 4470

Tyr Lys Met Tyr Glu Gly Gly Glu Pro Asp Asp Val Gly Gly Leu  
 4475 4480 4485

Leu Asp Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro Thr Asn Phe  
 4490 4495 4500

Thr Asn Pro Val Tyr Ala Thr Leu Tyr Met Gly Gly His Gly Ser  
 4505 4510 4515

Arg His Ser Leu Ala Ser Thr Asp Glu Lys Arg Glu Leu Leu Gly  
 4520 4525 4530

Arg Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala  
 4535 4540 4545

<210> 72  
 <211> 196  
 <212> PRT  
 <213> MOUSE

<400> 72

Leu Ser Ser Leu Ala Lys Pro Ser Glu Asn Gly Asn Gly Val Thr Phe  
 1 5 10 15

Arg Ser Gly Ala Asp Val Asn Met Asp Ile Gly Val Ser Pro Phe Gly  
 20 25 30

Pro Glu Thr Ile Ile Asp Arg Ser Met Ala Met Asn Glu Gln Phe Val  
 35 40 45

Met Glu Val Gly Lys Gln Pro Val Ile Phe Glu Asn Pro Met Tyr Ala  
 50 55 60

Ala Lys Asp Ser Thr Ser Lys Val Gly Leu Ala Val Gln Gly Pro Ser  
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65 70 75 80

Val Ser Ser Gln Val Thr Val Pro Glu Asn Val Glu Asn Gln Asn Tyr  
85 90 95

Gly Arg Ser Ile Asp Pro Ser Glu Ile Val Pro Glu Pro Lys Pro Ala  
100 105 110

Ser Pro Gly Ala Asp Glu Thr Gln Gly Thr Lys Trp Asn Ile Phe Lys  
115 120 125

Arg Lys Pro Lys Gln Thr Thr Asn Phe Glu Asn Pro Ile Tyr Ala Glu  
130 135 140

Met Asp Thr Glu Gln Lys Glu Ala Val Ala Val Ala Pro Pro Pro Ser  
145 150 155 160

Pro Ser Leu Pro Ala Lys Ala Ser Lys Arg Ser Ser Thr Pro Gly Tyr  
165 170 175

Thr Ala Thr Glu Asp Thr Phe Lys Asp Thr Ala Asn Leu Val Lys Glu  
180 185 190

Asp Ser Asp Val  
195

<210> 73  
 <211> 2867  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 73

Met Asp Arg Gly Pro Ala Ala Val Ala Cys Thr Leu Leu Leu Ala Leu  
1 5 10 15

Val Ala Cys Leu Ala Pro Ala Ser Gly Gln Glu Cys Asp Ser Ala His  
20 25 30

Phe Arg Cys Gly Ser Gly His Cys Ile Pro Ala Asp Trp Arg Cys Asp  
35 40 45

Gly Thr Lys Asp Cys Ser Asp Asp Ala Asp Glu Ile Gly Cys Ala Val  
50 55 60

Val Thr Cys Gln Gln Gly Tyr Phe Lys Cys Gln Ser Glu Gly Gln Cys  
65 70 75 80

Ile Pro Asn Ser Trp Val Cys Asp Gln Asp Gln Asp Cys Asp Asp Gly  
85 90 95

Ser Asp Glu Arg Gln Asp Cys Ser Gln Ser Thr Cys Ser Ser His Gln  
100 105 110

## Nonprovisional IP-017.ST25.txt

Ile Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp  
 115 120 125  
 His Val Arg Asp Cys Pro Asp Gly Ala Asp Glu Asn Asp Cys Gln Tyr  
 130 135 140  
 Pro Thr Cys Glu Gln Leu Thr Cys Asp Asn Gly Ala Cys Tyr Asn Thr  
 145 150 155 160  
 Ser Gln Lys Cys Asp Trp Lys Val Asp Cys Arg Asp Ser Ser Asp Glu  
 165 170 175  
 Ile Asn Cys Thr Glu Ile Cys Leu His Asn Glu Phe Ser Cys Gly Asn  
 180 185 190  
 Gly Glu Cys Ile Pro Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys  
 195 200 205  
 Gln Asp Gly Ser Asp Glu His Ala Cys Asn Tyr Pro Thr Cys Gly Gly  
 210 215 220  
 Tyr Gln Phe Thr Cys Pro Ser Gly Arg Cys Ile Tyr Gln Asn Trp Val  
 225 230 235 240  
 Cys Asp Gly Glu Asp Asp Cys Lys Asp Asn Gly Asp Glu Asp Gly Cys  
 245 250 255  
 Glu Ser Gly Pro His Asp Val His Lys Cys Ser Pro Arg Glu Trp Ser  
 260 265 270  
 Cys Pro Glu Ser Gly Arg Cys Ile Ser Ile Tyr Lys Val Cys Asp Gly  
 275 280 285  
 Ile Leu Asp Cys Pro Gly Arg Glu Asp Glu Asn Asn Thr Ser Thr Gly  
 290 295 300  
 Lys Tyr Cys Ser Met Thr Leu Cys Ser Ala Leu Asn Cys Gln Tyr Gln  
 305 310 315 320  
 Cys His Glu Thr Pro Tyr Gly Gly Ala Cys Phe Cys Pro Pro Gly Tyr  
 325 330 335  
 Ile Ile Asn His Asn Asp Ser Arg Thr Cys Val Glu Phe Asp Asp Cys  
 340 345 350  
 Gln Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Ser Arg Pro Gly Arg  
 355 360 365  
 His Leu Cys His Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln Tyr  
 370 375 380

## Nonprovisional IP-017.ST25.txt

Cys Lys Ala Asn Asp Ser Phe Gly Glu Ala Ser Ile Ile Phe Ser Asn  
 385 390 395 400  
 Gly Arg Asp Leu Leu Ile Gly Asp Ile His Gly Arg Ser Phe Arg Ile  
 405 410 415  
 Leu Val Glu Ser Gln Asn Arg Gly Val Ala Val Gly Val Ala Phe His  
 420 425 430  
 Tyr His Leu Gln Arg Val Phe Trp Thr Asp Thr Val Gln Asn Lys Val  
 435 440 445  
 Phe Ser Val Asp Ile Asn Gly Leu Asn Ile Gln Glu Val Leu Asn Val  
 450 455 460  
 Ser Val Glu Thr Pro Glu Asn Leu Ala Val Asp Trp Val Asn Asn Lys  
 465 470 475 480  
 Ile Tyr Leu Val Glu Thr Lys Val Asn Arg Ile Asp Met Val Asn Leu  
 485 490 495  
 Asp Gly Ser Tyr Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro  
 500 505 510  
 Arg Gly Ile Ala Val Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp  
 515 520 525  
 Trp Glu Ser Leu Ser Gly Glu Pro Lys Leu Glu Arg Ala Phe Met Asp  
 530 535 540  
 Gly Ser Asn Arg Lys Asp Leu Val Lys Thr Lys Leu Gly Trp Pro Ala  
 545 550 555 560  
 Gly Val Thr Leu Asp Met Ile Ser Lys Arg Val Tyr Trp Val Asp Ser  
 565 570 575  
 Arg Phe Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys  
 580 585 590  
 Thr Val Val His Gly Gly Ser Leu Ile Pro His Pro Phe Gly Val Ser  
 595 600 605  
 Leu Phe Glu Gly Gln Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val  
 610 615 620  
 Leu Lys Ala Asn Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr Tyr Gln  
 625 630 635 640  
 Ala Ser Leu Arg Pro Tyr Gly Val Thr Val Tyr His Ser Leu Arg Gln  
 645 650 655

## Nonprovisional IP-017.ST25.txt

Pro Tyr Ala Thr Asn Pro Cys Lys Asp Asn Asn Gly Gly Cys Glu Gln  
 660 665 670  
 Val Cys Val Leu Ser His Arg Thr Asp Asn Asp Gly Leu Gly Phe Arg  
 675 680 685  
 Cys Lys Cys Thr Phe Gly Phe Gln Leu Asp Thr Asp Glu Arg His Cys  
 690 695 700  
 Ile Ala Val Gln Asn Phe Leu Ile Phe Ser Ser Gln Val Ala Ile Arg  
 705 710 715 720  
 Gly Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val  
 725 730 735  
 Ser Gly Asn Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln Asp  
 740 745 750  
 Ser Thr Ile Phe Phe Ser Asp Met Ser Lys His Met Ile Phe Lys Gln  
 755 760 765  
 Lys Ile Asp Gly Thr Gly Arg Glu Ile Leu Ala Ala Asn Arg Val Glu  
 770 775 780  
 Asn Val Glu Ser Leu Ala Phe Asp Trp Ile Ser Lys Asn Leu Tyr Trp  
 785 790 795 800  
 Thr Asp Ser His Tyr Lys Ser Ile Ser Val Met Arg Leu Ala Asp Lys  
 805 810 815  
 Thr Arg Arg Thr Val Val Gln Tyr Leu Asn Asn Pro Arg Ser Val Val  
 820 825 830  
 Val His Pro Phe Ala Gly Tyr Leu Phe Phe Thr Asp Trp Phe Arg Pro  
 835 840 845  
 Ala Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Leu Pro Val  
 850 855 860  
 Ile Asn Thr Thr Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ala  
 865 870 875 880  
 Ala Ser Arg Leu Tyr Trp Val Asp Ala Tyr Phe Asp Lys Ile Glu His  
 885 890 895  
 Ser Thr Phe Asp Gly Leu Asp Arg Arg Arg Leu Gly His Ile Glu Gln  
 900 905 910  
 Met Thr His Pro Phe Gly Leu Ala Ile Phe Gly Glu His Leu Phe Phe  
 915 920 925

## Nonprovisional IP-017.ST25.txt

Thr Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ala Asp Gly  
 930 935 940  
 Gly Glu Met Thr Val Ile Arg Ser Gly Ile Ala Tyr Ile Leu His Leu  
 945 950 955 960  
 Lys Ser Tyr Asp Val Asn Ile Gln Thr Gly Ser Asn Ala Cys Asn Gln  
 965 970 975  
 Pro Thr His Pro Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro  
 980 985 990  
 Asn Phe Gln Arg Val Cys Gly Cys Pro Tyr Gly Met Arg Leu Ala Ser  
 995 1000 1005  
 Asn His Leu Thr Cys Glu Gly Asp Pro Thr Asn Glu Pro Pro Thr  
 1010 1015 1020  
 Glu Gln Cys Gly Leu Phe Ser Phe Pro Cys Lys Asn Gly Arg Cys  
 1025 1030 1035  
 Val Pro Asn Tyr Tyr Leu Cys Asp Gly Val Asp Asp Cys His Asp  
 1040 1045 1050  
 Asn Ser Asp Glu Gln Leu Cys Gly Thr Leu Asn Asn Thr Cys Ser  
 1055 1060 1065  
 Ser Ser Ala Phe Thr Cys Gly His Gly Glu Cys Ile Pro Ala His  
 1070 1075 1080  
 Trp Arg Cys Asp Lys Arg Asn Asp Cys Val Asp Gly Ser Asp Glu  
 1085 1090 1095  
 His Asn Cys Pro Thr His Ala Pro Ala Ser Cys Leu Asp Thr Gln  
 1100 1105 1110  
 Tyr Thr Cys Asp Asn His Gln Cys Ile Ser Lys Asn Trp Val Cys  
 1115 1120 1125  
 Asp Thr Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu Lys Asn Cys  
 1130 1135 1140  
 Asn Ser Thr Glu Thr Cys Gln Pro Ser Gln Phe Asn Cys Pro Asn  
 1145 1150 1155  
 His Arg Cys Ile Asp Leu Ser Phe Val Cys Asp Gly Asp Lys Asp  
 1160 1165 1170  
 Cys Val Asp Gly Ser Asp Glu Val Gly Cys Val Leu Asn Cys Thr  
 1175 1180 1185

## Nonprovisional IP-017.ST25.txt

Ala Ser Gln Phe Lys Cys Ala Ser Gly Asp Lys Cys Ile Gly Val  
 1190 1195 1200  
 Thr Asn Arg Cys Asp Gly Val Phe Asp Cys Ser Asp Asn Ser Asp  
 1205 1210 1215  
 Glu Ala Gly Cys Pro Thr Arg Pro Pro Gly Met Cys His Ser Asp  
 1220 1225 1230  
 Glu Phe Gln Cys Gln Glu Asp Gly Ile Cys Ile Pro Asn Phe Trp  
 1235 1240 1245  
 Glu Cys Asp Gly His Pro Asp Cys Leu Tyr Gly Ser Asp Glu His  
 1250 1255 1260  
 Asn Ala Cys Val Pro Lys Thr Cys Pro Ser Ser Tyr Phe His Cys  
 1265 1270 1275  
 Asp Asn Gly Asn Cys Ile His Arg Ala Trp Leu Cys Asp Arg Asp  
 1280 1285 1290  
 Asn Asp Cys Gly Asp Met Ser Asp Glu Lys Asp Cys Pro Thr Gln  
 1295 1300 1305  
 Pro Phe Arg Cys Pro Ser Trp Gln Trp Gln Cys Leu Gly His Asn  
 1310 1315 1320  
 Ile Cys Val Asn Leu Ser Val Val Cys Asp Gly Ile Phe Asp Cys  
 1325 1330 1335  
 Pro Asn Gly Thr Asp Glu Ser Pro Leu Cys Asn Gly Asn Ser Cys  
 1340 1345 1350  
 Ser Asp Phe Asn Gly Gly Cys Thr His Glu Cys Val Gln Glu Pro  
 1355 1360 1365  
 Phe Gly Ala Lys Cys Leu Cys Pro Leu Gly Phe Leu Leu Ala Asn  
 1370 1375 1380  
 Asp Ser Lys Thr Cys Glu Asp Ile Asp Glu Cys Asp Ile Leu Gly  
 1385 1390 1395  
 Ser Cys Ser Gln His Cys Tyr Asn Met Arg Gly Ser Phe Arg Cys  
 1400 1405 1410  
 Ser Cys Asp Thr Gly Tyr Met Leu Glu Ser Asp Gly Arg Thr Cys  
 1415 1420 1425  
 Lys Val Thr Ala Ser Glu Ser Leu Leu Leu Leu Val Ala Ser Gln  
 1430 1435 1440



## Nonprovisional IP-017.ST25.txt

Asn Lys Ile Ile Ala Asp Ser Val Thr Ser Gln Val His Asn Ile  
 1445 1455  
 Tyr Ser Leu Val Glu Asn Gly Ser Tyr Ile Val Ala Val Asp Phe  
 1460 1465 1470  
 Asp Ser Ile Ser Gly Arg Ile Phe Trp Ser Asp Ala Thr Gln Gly  
 1475 1480 1485  
 Lys Thr Trp Ser Ala Phe Gln Asn Gly Thr Asp Arg Arg Val Val  
 1490 1495 1500  
 Phe Asp Ser Ser Ile Ile Leu Thr Glu Thr Ile Ala Ile Asp Trp  
 1505 1515  
 Val Gly Arg Asn Leu Tyr Trp Thr Asp Tyr Ala Leu Glu Thr Ile  
 1520 1525 1530  
 Glu Val Ser Lys Ile Asp Gly Ser His Arg Thr Val Leu Ile Ser  
 1535 1540 1545  
 Lys Asn Leu Thr Asn Pro Arg Gly Leu Ala Leu Asp Pro Arg Met  
 1550 1555 1560  
 Asn Glu His Leu Leu Phe Trp Ser Asp Trp Gly His His Pro Arg  
 1565 1570 1575  
 Ile Glu Arg Ala Ser Met Asp Gly Ser Met Arg Thr Val Ile Val  
 1580 1585 1590  
 Gln Asp Lys Ile Phe Trp Pro Cys Gly Leu Thr Ile Asp Tyr Pro  
 1595 1600 1605  
 Asn Arg Leu Leu Tyr Phe Met Asp Ser Tyr Leu Asp Tyr Met Asp  
 1610 1615 1620  
 Phe Cys Asp Tyr Asn Gly His His Arg Arg Gln Val Ile Ala Ser  
 1625 1630 1635  
 Asp Leu Ile Ile Arg His Pro Tyr Ala Leu Thr Leu Phe Glu Asp  
 1640 1645 1650  
 Ser Val Tyr Trp Thr Asp Arg Ala Thr Arg Arg Val Met Arg Ala  
 1655 1660 1665  
 Asn Lys Trp His Gly Gly Asn Gln Ser Val Val Met Tyr Asn Ile  
 1670 1675 1680  
 Gln Trp Pro Leu Gly Ile Val Ala Val His Pro Ser Lys Gln Pro  
 1685 1690 1695

## Nonprovisional IP-017.ST25.txt

Asn Ser Val Asn Pro Cys Ala Phe Ser Arg Cys Ser His Leu Cys  
 1700 1705 1710  
 Leu Leu Ser Ser Gln Gly Pro His Phe Tyr Ser Cys Val Cys Pro  
 1715 1720 1725  
 Ser Gly Trp Ser Leu Ser Pro Asp Leu Leu Asn Cys Leu Arg Asp  
 1730 1735 1740  
 Asp Gln Pro Phe Leu Ile Thr Val Arg Gln His Ile Ile Phe Gly  
 1745 1750 1755  
 Ile Ser Leu Asn Pro Glu Val Lys Ser Asn Asp Ala Met Val Pro  
 1760 1765 1770  
 Ile Ala Gly Ile Gln Asn Gly Leu Asp Val Glu Phe Asp Asp Ala  
 1775 1780 1785  
 Glu Gln Tyr Ile Tyr Trp Val Glu Asn Pro Gly Glu Ile His Arg  
 1790 1795 1800  
 Val Lys Thr Asp Gly Thr Asn Arg Thr Val Phe Ala Ser Ile Ser  
 1805 1810 1815  
 Met Val Gly Pro Ser Met Asn Leu Ala Leu Asp Trp Ile Ser Arg  
 1820 1825 1830  
 Asn Leu Tyr Ser Thr Asn Pro Arg Thr Gln Ser Ile Glu Val Leu  
 1835 1840 1845  
 Thr Leu His Gly Asp Ile Arg Tyr Arg Lys Thr Leu Ile Ala Asn  
 1850 1855 1860  
 Asp Gly Thr Ala Leu Gly Val Gly Phe Pro Ile Gly Ile Thr Val  
 1865 1870 1875  
 Asp Pro Ala Arg Gly Lys Leu Tyr Trp Ser Asp Gln Gly Thr Asp  
 1880 1885 1890  
 Ser Gly Val Pro Ala Lys Ile Ala Ser Ala Asn Met Asp Gly Thr  
 1895 1900 1905  
 Ser Val Lys Thr Leu Phe Thr Gly Asn Leu Glu His Leu Glu Cys  
 1910 1915 1920  
 Val Thr Leu Asp Ile Glu Glu Gln Lys Leu Tyr Trp Ala Val Thr  
 1925 1930 1935  
 Gly Arg Gly Val Ile Glu Arg Gly Asn Val Asp Gly Thr Asp Arg  
 1940 1945 1950

## Nonprovisional IP-017.ST25.txt

Met Ile Leu Val His Gln Leu Ser His Pro Trp Gly Ile Ala Val  
 1955 1960 1965  
 His Asp Ser Phe Leu Tyr Tyr Thr Asp Glu Gln Tyr Glu Val Ile  
 1970 1975 1980  
 Glu Arg Val Asp Lys Ala Thr Gly Ala Asn Lys Ile Val Leu Arg  
 1985 1990 1995  
 Asp Asn Val Pro Asn Leu Arg Gly Leu Gln Val Tyr His Arg Arg  
 2000 2005 2010  
 Asn Ala Ala Glu Ser Ser Asn Gly Cys Ser Asn Asn Met Asn Ala  
 2015 2020 2025  
 Cys Gln Gln Ile Cys Leu Pro Val Pro Gly Gly Leu Phe Ser Cys  
 2030 2035 2040  
 Ala Cys Ala Thr Gly Phe Lys Leu Asn Pro Asp Asn Arg Ser Cys  
 2045 2050 2055  
 Ser Pro Tyr Asn Ser Phe Ile Val Val Ser Met Leu Ser Ala Ile  
 2060 2065 2070  
 Arg Gly Phe Ser Leu Glu Leu Ser Asp His Ser Glu Thr Met Val  
 2075 2080 2085  
 Pro Val Ala Gly Gln Gly Arg Asn Ala Leu His Val Asp Val Asp  
 2090 2095 2100  
 Val Ser Ser Gly Phe Ile Tyr Trp Cys Asp Phe Ser Ser Ser Val  
 2105 2110 2115  
 Ala Ser Asp Asn Ala Ile Arg Arg Ile Lys Pro Asp Gly Ser Ser  
 2120 2125 2130  
 Leu Met Asn Ile Val Thr His Gly Ile Gly Glu Asn Gly Val Arg  
 2135 2140 2145  
 Gly Ile Ala Val Asp Trp Val Ala Gly Asn Leu Tyr Phe Thr Asn  
 2150 2155 2160  
 Ala Phe Val Ser Glu Thr Leu Ile Glu Val Leu Arg Ile Asn Thr  
 2165 2170 2175  
 Thr Tyr Arg Arg Val Leu Leu Lys Val Thr Val Asp Met Pro Arg  
 2180 2185 2190  
 His Ile Val Val Asp Pro Lys Asn Arg Tyr Leu Phe Trp Ala Asp  
 2195 2200 2205

## Nonprovisional IP-017.ST25.txt

Tyr Gly Gln Arg Pro Lys Ile Glu Arg Ser Phe Leu Asp Cys Thr  
 2210 2215 2220  
 Asn Arg Thr Val Leu Val Ser Glu Gly Ile Val Thr Pro Arg Gly  
 2225 2230 2235  
 Leu Ala Val Asp Arg Ser Asp Gly Tyr Val Tyr Trp Val Asp Asp  
 2240 2245 2250  
 Ser Leu Asp Ile Ile Ala Arg Ile Arg Ile Asn Gly Glu Asn Ser  
 2255 2260 2265  
 Glu Val Ile Arg Tyr Gly Ser Arg Tyr Pro Thr Pro Tyr Gly Ile  
 2270 2275 2280  
 Thr Val Phe Glu Asn Ser Ile Ile Trp Val Asp Arg Asn Leu Lys  
 2285 2290 2295  
 Lys Ile Phe Gln Ala Ser Lys Glu Pro Glu Asn Thr Glu Pro Pro  
 2300 2305 2310  
 Thr Val Ile Arg Asp Asn Ile Asn Trp Leu Arg Asp Val Thr Ile  
 2315 2320 2325  
 Phe Asp Lys Gln Val Gln Pro Arg Ser Pro Ala Glu Val Asn Asn  
 2330 2335 2340  
 Asn Pro Cys Leu Glu Asn Asn Gly Gly Cys Ser His Leu Cys Phe  
 2345 2350 2355  
 Ala Leu Pro Gly Leu His Thr Pro Lys Cys Asp Cys Ala Phe Gly  
 2360 2365 2370  
 Thr Leu Gln Ser Asp Gly Lys Asn Cys Ala Ile Ser Thr Glu Asn  
 2375 2380 2385  
 Phe Leu Ile Phe Ala Leu Ser Asn Ser Leu Arg Ser Leu His Leu  
 2390 2395 2400  
 Asp Pro Glu Asn His Ser Pro Pro Phe Gln Thr Ile Asn Val Glu  
 2405 2410 2415  
 Arg Thr Val Met Ser Leu Asp Tyr Asp Ser Val Ser Asp Arg Ile  
 2420 2425 2430  
 Tyr Phe Thr Gln Asn Leu Ala Ser Gly Val Gly Gln Ile Ser Tyr  
 2435 2440 2445  
 Ala Thr Leu Ser Ser Gly Ile His Thr Pro Thr Val Ile Ala Ser  
 2450 2455 2460

## Nonprovisional IP-017.ST25.txt

Gly Ile Gly Thr Ala Asp Gly Ile Ala Phe Asp Trp Ile Thr Arg  
 2465 2470 2475  
 Arg Ile Tyr Tyr Ser Asp Tyr Leu Asn Gln Met Ile Asn Ser Met  
 2480 2485 2490  
 Ala Glu Asp Gly Ser Asn Arg Thr Val Ile Ala Arg Val Pro Lys  
 2495 2500 2505  
 Pro Arg Ala Ile Val Leu Asp Pro Cys Gln Gly Tyr Leu Tyr Trp  
 2510 2515 2520  
 Ala Asp Trp Asp Thr His Ala Lys Ile Glu Arg Ala Thr Leu Gly  
 2525 2530 2535  
 Gly Asn Phe Arg Val Pro Ile Val Asn Ser Ser Leu Val Met Pro  
 2540 2545 2550  
 Ser Gly Leu Thr Leu Asp Tyr Glu Glu Asp Leu Leu Tyr Trp Val  
 2555 2560 2565  
 Asp Ala Ser Leu Gln Arg Ile Glu Arg Ser Thr Leu Thr Gly Val  
 2570 2575 2580  
 Asp Arg Glu Val Ile Val Asn Ala Ala Val His Ala Phe Gly Leu  
 2585 2590 2595  
 Thr Leu Tyr Gly Gln Tyr Ile Tyr Trp Thr Asp Leu Tyr Thr Gln  
 2600 2605 2610  
 Arg Ile Tyr Arg Ala Asn Lys Tyr Asp Gly Ser Gly Gln Ile Ala  
 2615 2620 2625  
 Met Thr Thr Asn Leu Leu Ser Gln Pro Arg Gly Ile Asn Thr Val  
 2630 2635 2640  
 Val Lys Asn Gln Lys Gln Gln Cys Asn Asn Pro Cys Glu Gln Phe  
 2645 2650 2655  
 Asn Gly Gly Cys Ser His Ile Cys Ala Pro Gly Pro Asn Gly Ala  
 2660 2665 2670  
 Glu Cys Gln Cys Pro His Glu Gly Asn Trp Tyr Leu Ala Asn Asn  
 2675 2680 2685  
 Arg Lys His Cys Ile Val Asp Asn Gly Glu Arg Cys Gly Ala Ser  
 2690 2695 2700  
 Ser Phe Thr Cys Ser Asn Gly Arg Cys Ile Ser Glu Glu Trp Lys  
 2705 2710 2715

## Nonprovisional IP-017.ST25.txt

Cys Asp Asn Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu Met Glu  
2720 2725 2730

Ser Val Cys Ala Leu His Thr Cys Ser Pro Thr Ala Phe Thr Cys  
2735 2740 2745

Ala Asn Gly Arg Cys Val Gln Tyr Ser Tyr Arg Cys Asp Tyr Tyr  
2750 2755 2760

Asn Asp Cys Gly Asp Gly Ser Asp Glu Ala Gly Cys Leu Phe Arg  
2765 2770 2775

Asp Cys Asn Ala Thr Thr Glu Phe Met Cys Asn Asn Arg Arg Cys  
2780 2785 2790

Ile Pro Arg Glu Phe Ile Cys Asn Gly Val Asp Asn Cys His Asp  
2795 2800 2805

Asn Asn Thr Ser Asp Glu Lys Asn Cys Pro Asp Arg Thr Cys Gln  
2810 2815 2820

Ser Gly Tyr Thr Lys Cys His Asn Ser Asn Ile Cys Ile Pro Arg  
2825 2830 2835

Val Tyr Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Asn Ser Asp  
2840 2845 2850

Glu Asn Pro Thr Tyr Cys Ser His Ser His Val Gln Gln Gln  
2855 2860 2865

<210> 74  
<211> 4660  
<212> PRT  
<213> RAT

<400> 74

Met Glu Arg Gly Ala Ala Ala Ala Ala Trp Met Leu Leu Leu Ala Ile  
1 5 10 15

Ala Ala Cys Leu Glu Pro Val Ser Ser Gln Glu Cys Gly Ser Gly Asn  
20 25 30

Phe Arg Cys Asp Asn Gly Tyr Cys Ile Pro Ala Ser Trp Arg Cys Asp  
35 40 45

Gly Thr Arg Asp Cys Leu Asp Asp Thr Asp Glu Ile Gly Cys Pro Pro  
50 55 60

Arg Ser Cys Glu Ser Gly Leu Phe Leu Cys Pro Ala Glu Gly Thr Cys  
65 70 75 80

## Nonprovisional IP-017.ST25.txt

Ile Pro Ser Ser Trp Val Cys Asp Glu Asp Lys Asp Cys Ser Asp Gly  
 85 90 95  
 Ala Asp Glu Gln Gln Asn Cys Ala Gly Thr Thr Cys Ser Ala Gln Gln  
 100 105 110  
 Met Thr Cys Ser Asn Gly Gln Cys Ile Pro Ser Glu Tyr Arg Cys Asp  
 115 120 125  
 His Val Ser Asp Cys Pro Asp Gly Ser Asp Glu Arg Asn Cys His Tyr  
 130 135 140  
 Pro Thr Cys Asp Gln Leu Thr Cys Ala Asn Gly Ala Cys Tyr Asn Thr  
 145 150 155 160  
 Ser Gln Arg Cys Asp Gln Lys Val Asp Cys Arg Asp Ser Ser Asp Glu  
 165 170 175  
 Ala Asn Cys Thr Thr Leu Cys Ser Gln Lys Glu Phe Glu Cys Gly Ser  
 180 185 190  
 Gly Glu Cys Ile Leu Arg Ala Tyr Val Cys Asp His Asp Asn Asp Cys  
 195 200 205  
 Glu Asp Asn Ser Asp Glu Arg Asn Cys Asn Tyr Asp Thr Cys Gly Gly  
 210 215 220  
 His Gln Phe Thr Cys Ser Asn Gly Gln Cys Ile Asn Gln Asn Trp Val  
 225 230 235 240  
 Cys Asp Gly Asp Asp Asp Cys Gln Asp Ser Gly Asp Glu Asp Gly Cys  
 245 250 255  
 Glu Ser Asn Gln Ser His His Arg Cys Tyr Pro Arg Glu Trp Ala Cys  
 260 265 270  
 Pro Gly Ser Gly Arg Cys Ile Ser Ile Asp Lys Val Cys Asp Gly Val  
 275 280 285  
 Pro Asp Cys Pro Glu Gly Asp Asp Glu Asn Asn Val Thr Ser Gly Arg  
 290 295 300  
 Thr Cys Gly Met Gly Val Cys Ser Val Leu Asn Cys Glu Tyr Gln Cys  
 305 310 315 320  
 His Gln Thr Pro Phe Gly Gly Glu Cys Phe Cys Pro Pro Gly His Ile  
 325 330 335  
 Ile Asn Ser Asn Asp Ser Arg Thr Cys Ile Asp Phe Asp Asp Cys Gln  
 340 345 350

## Nonprovisional IP-017.ST25.txt

Ile Trp Gly Ile Cys Asp Gln Lys Cys Glu Asn Arg Gln Gly Arg His  
 355 360 365  
 Gln Cys Leu Cys Glu Glu Gly Tyr Ile Leu Glu Arg Gly Gln His Cys  
 370 375 380  
 Lys Ser Ser Asp Ser Phe Ser Ala Ala Ser Val Ile Phe Ser Asn Gly  
 385 390 395 400  
 Arg Asp Leu Leu Val Gly Asp Leu His Gly Arg Asn Phe Arg Ile Leu  
 405 410 415  
 Ala Glu Ser Lys Asn Arg Gly Met Val Met Gly Val Asp Phe His Tyr  
 420 425 430  
 Gln Lys His Arg Val Phe Trp Thr Asp Pro Met Gln Glu Lys Val Phe  
 435 440 445  
 Ser Thr Asp Ile Asn Gly Leu Asn Thr Gln Glu Ile Leu Asn Val Ser  
 450 455 460  
 Val Asp Thr Pro Glu Asn Leu Ala Val Asp Trp Ile Asn Asn Lys Leu  
 465 470 475 480  
 Tyr Leu Val Glu Thr Lys Val Asn Arg Ile Asp Val Val Asn Leu Glu  
 485 490 495  
 Gly Asn Gln Arg Val Thr Leu Ile Thr Glu Asn Leu Gly His Pro Arg  
 500 505 510  
 Gly Ile Ala Leu Asp Pro Thr Val Gly Tyr Leu Phe Phe Ser Asp Trp  
 515 520 525  
 Gly Ser Leu Ser Gly Gln Pro Lys Val Glu Arg Ala Phe Met Asp Gly  
 530 535 540  
 Ser Asn Arg Lys Asp Leu Val Thr Thr Lys Val Gly Trp Pro Ala Gly  
 545 550 555 560  
 Ile Thr Leu Asp Leu Val Ser Lys Arg Val Tyr Trp Val Asp Ser Arg  
 565 570 575  
 Tyr Asp Tyr Ile Glu Thr Val Thr Tyr Asp Gly Ile Gln Arg Lys Thr  
 580 585 590  
 Val Ala Arg Gly Gly Ser Leu Val Pro His Pro Phe Gly Ile Ser Leu  
 595 600 605  
 Phe Glu Glu His Val Phe Phe Thr Asp Trp Thr Lys Met Ala Val Met  
 610 615 620



## Nonprovisional IP-017.ST25.txt

Lys Ala Ser Lys Phe Thr Glu Thr Asn Pro Gln Val Tyr His Gln Ser  
 625 630 635 640  
 Ser Leu Arg Pro His Gly Val Thr Val Tyr His Ala Leu Arg Gln Pro  
 645 650 655  
 Asn Ala Thr Asn Pro Cys Gly Ser Asn Asn Gly Gly Cys Ala Gln Val  
 660 665 670  
 Cys Val Leu Ser His Arg Thr Asp Asn Gly Gly Leu Gly Tyr Arg Cys  
 675 680 685  
 Lys Cys Glu Phe Gly Phe Glu Leu Asp Asp Asp Glu His Arg Cys Val  
 690 695 700  
 Ala Val Lys Asn Phe Leu Leu Phe Ser Ser Lys Thr Ala Val Arg Gly  
 705 710 715 720  
 Ile Pro Phe Thr Leu Ser Thr Gln Glu Asp Val Met Val Pro Val Thr  
 725 730 735  
 Gly Ser Pro Ser Phe Phe Val Gly Ile Asp Phe Asp Ala Gln His Ser  
 740 745 750  
 Thr Val Phe Tyr Ser Asp Leu Ser Lys Asp Ile Ile Tyr Lys Gln Lys  
 755 760 765  
 Ile Asp Gly Thr Gly Lys Glu Val Ile Thr Ala Asn Arg Leu Glu Ser  
 770 775 780  
 Val Glu Cys Leu Thr Phe Asp Trp Ile Ser Arg Asn Leu Tyr Trp Thr  
 785 790 795 800  
 Asp Gly Gly Leu Lys Ser Val Thr Val Leu Arg Leu Ala Asp Lys Ser  
 805 810 815  
 Arg Arg Gln Ile Ile Ser Asn Leu Asn Asn Pro Arg Ser Ile Val Val  
 820 825 830  
 His Pro Thr Ala Gly Tyr Met Phe Leu Ser Asp Trp Phe Arg Pro Ala  
 835 840 845  
 Lys Ile Met Arg Ala Trp Ser Asp Gly Ser His Leu Met Pro Ile Val  
 850 855 860  
 Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Ile Asp Trp Ser Ala  
 865 870 875 880  
 Ser Arg Leu Tyr Trp Val Asp Ala Phe Phe Asp Lys Ile Glu His Ser  
 885 890 895

## Nonprovisional IP-017.ST25.txt

Thr Leu Asp Gly Leu Asp Arg Lys Arg Leu Gly His Val Asp Gln Met  
 900 905 910  
 Thr His Pro Phe Gly Leu Thr Val Phe Lys Asp Asn Val Phe Ile Thr  
 915 920 925  
 Asp Trp Arg Leu Gly Ala Ile Ile Arg Val Arg Lys Ser Asp Gly Gly  
 930 935 940  
 Asp Met Thr Val Ile Arg Arg Gly Ile Ser Ser Val Met His Val Lys  
 945 950 955 960  
 Ala Tyr Asp Ala Asp Leu Gln Thr Gly Ser Asn Tyr Cys Ser Gln Thr  
 965 970 975  
 Thr His Ala Asn Gly Asp Cys Ser His Phe Cys Phe Pro Val Pro Asn  
 980 985 990  
 Phe Gln Arg Val Cys Gly Cys Pro Tyr Gly Met Lys Leu Gln Arg Asp  
 995 1000 1005  
 Gln Met Thr Cys Glu Gly Asp Pro Ala Arg Glu Pro Pro Thr Gln  
 1010 1015 1020  
 Gln Cys Gly Ser Leu Ser Phe Pro Cys Asn Asn Gly Lys Cys Val  
 1025 1030 1035  
 Pro Ser Phe Phe Arg Cys Asp Gly Val Asp Asp Cys His Asp Asn  
 1040 1045 1050  
 Ser Asp Glu His Gln Cys Gly Val Phe Asn Asn Thr Cys Ser Pro  
 1055 1060 1065  
 Ser Ala Phe Ala Cys Val Arg Gly Gly Gln Cys Ile Pro Gly Gln  
 1070 1075 1080  
 Trp His Cys Asp Arg Gln Asn Asp Cys Leu Asp Gly Ser Asp Glu  
 1085 1090 1095  
 Gln Asn Cys Pro Thr His Ala Thr Ser Ser Thr Cys Pro Ser Thr  
 1100 1105 1110  
 Ser Phe Thr Cys Asp Asn His Val Cys Ile Pro Lys Asp Trp Val  
 1115 1120 1125  
 Cys Asp Thr Asp Asn Asp Cys Ser Asp Gly Ser Asp Glu Lys Asn  
 1130 1135 1140  
 Cys Gln Ala Ser Gly Thr Cys Gln Pro Thr Gln Phe Arg Cys Pro  
 1145 1150 1155

## Nonprovisional IP-017.ST25.txt

Asp His Arg Cys Ile Ser Pro Leu Tyr Val Cys Asp Gly Asp Lys  
 1160 1165 1170  
 Asp Cys Ala Asp Gly Ser Asp Glu Ala Gly Cys Val Leu Asn Cys  
 1175 1180 1185  
 Thr Ser Ala Gln Phe Lys Cys Ala Asp Gly Ser Ser Cys Ile Asn  
 1190 1195 1200  
 Ser Arg Tyr Arg Cys Asp Gly Val Tyr Asp Cys Arg Asp Asn Ser  
 1205 1210 1215  
 Asp Glu Ala Gly Cys Pro Thr Arg Pro Pro Gly Met Cys His Pro  
 1220 1225 1230  
 Asp Glu Phe Gln Cys Gln Gly Asp Gly Thr Cys Ile Pro Asn Thr  
 1235 1240 1245  
 Trp Glu Cys Asp Gly His Pro Asp Cys Ile His Gly Ser Asp Glu  
 1250 1255 1260  
 His Thr Gly Cys Val Pro Lys Thr Cys Ser Pro Thr His Phe Leu  
 1265 1270 1275  
 Cys Asp Asn Gly Asn Cys Ile Tyr Lys Ala Trp Ile Cys Asp Gly  
 1280 1285 1290  
 Asp Asn Asp Cys Arg Asp Met Ser Asp Glu Lys Asp Cys Pro Thr  
 1295 1300 1305  
 Gln Pro Phe His Cys Pro Ser Thr Gln Trp Gln Cys Pro Gly Tyr  
 1310 1315 1320  
 Ser Thr Cys Ile Asn Leu Ser Ala Leu Cys Asp Gly Val Phe Asp  
 1325 1330 1335  
 Cys Pro Asn Gly Thr Asp Glu Ser Pro Leu Cys Asn Gln Asp Ser  
 1340 1345 1350  
 Cys Ser His Phe Asn Gly Gly Cys Thr His Gln Cys Met Gln Gly  
 1355 1360 1365  
 Pro Phe Gly Ala Thr Cys Leu Cys Pro Leu Gly Tyr Gln Leu Ala  
 1370 1375 1380  
 Asn Asp Thr Lys Thr Cys Glu Asp Ile Asn Glu Cys Asp Ile Pro  
 1385 1390 1395  
 Gly Phe Cys Ser Gln His Cys Val Asn Met Arg Gly Ser Phe Arg  
 1400 1405 1410

## Nonprovisional IP-017.ST25.txt

Cys Ala Cys Asp Pro Glu Tyr Thr Leu Glu Ser Asp Gly Arg Thr  
 1415 1420 1425  
 Cys Lys Val Thr Gly Ser Glu Asn Pro Leu Leu Val Val Ala Ser  
 1430 1435 1440  
 Arg Asp Lys Ile Ile Val Asp Asn Ile Thr Ala His Thr His Asn  
 1445 1450 1455  
 Leu Tyr Ser Leu Val Gln Asp Val Ser Phe Val Val Ala Leu Asp  
 1460 1465 1470  
 Phe Asp Ser Val Thr Gly Arg Val Phe Trp Ser Asp Leu Leu Gln  
 1475 1480 1485  
 Gly Lys Thr Trp Ser Val Phe Gln Asn Gly Thr Asp Lys Arg Val  
 1490 1495 1500  
 Val His Asp Ser Gly Leu Ser Val Thr Glu Met Ile Ala Val Asp  
 1505 1510 1515  
 Trp Ile Gly Arg Asn Leu Tyr Trp Thr Asp Tyr Ala Leu Glu Thr  
 1520 1525 1530  
 Ile Glu Val Ser Lys Ile Asp Gly Ser His Arg Thr Val Leu Ile  
 1535 1540 1545  
 Ser Lys Asn Val Thr Lys Pro Arg Gly Leu Ala Leu Asp Pro Arg  
 1550 1555 1560  
 Met Gly Asp Asn Val Met Phe Trp Ser Asp Trp Gly His His Pro  
 1565 1570 1575  
 Arg Ile Glu Arg Ala Ser Met Asp Gly Thr Met Arg Thr Val Ile  
 1580 1585 1590  
 Val Gln Glu Lys Ile Tyr Trp Pro Cys Gly Leu Ser Ile Asp Tyr  
 1595 1600 1605  
 Pro Asn Arg Leu Ile Tyr Phe Met Asp Ala Tyr Leu Asp Tyr Ile  
 1610 1615 1620  
 Glu Phe Cys Asp Tyr Asp Gly His Asn Arg Arg Gln Val Ile Ala  
 1625 1630 1635  
 Ser Asp Leu Val Leu His His Pro His Ala Leu Thr Leu Phe Glu  
 1640 1645 1650  
 Asp Phe Val Tyr Trp Thr Asp Arg Gly Thr Arg Gln Val Met Gln  
 1655 1660 1665

## Nonprovisional IP-017.ST25.txt

Ala Asn Lys Trp His Gly Gly Asn Gln Ser Val Val Met Tyr Ser  
 1670 1675 1680  
 Val His Gln Pro Leu Gly Ile Thr Ala Ile His Pro Ser Arg Gln  
 1685 1690 1695  
 Pro Pro Ser Arg Asn Pro Cys Ala Ser Ala Ser Cys Ser His Leu  
 1700 1705 1710  
 Cys Leu Leu Ser Ala Gln Ala Pro Arg His Tyr Ser Cys Ala Cys  
 1715 1720 1725  
 Pro Ser Gly Trp Asn Leu Ser Asp Asp Ser Val Asn Cys Val Arg  
 1730 1735 1740  
 Gly Asp Gln Pro Phe Leu Met Ser Val Arg Asp Asn Ile Ile Phe  
 1745 1750 1755  
 Gly Ile Ser Leu Asp Pro Glu Val Lys Ser Asn Asp Ala Met Val  
 1760 1765 1770  
 Pro Ile Ser Gly Ile Gln His Gly Tyr Asp Val Glu Phe Asp Asp  
 1775 1780 1785  
 Ser Glu Gln Phe Ile Tyr Trp Val Glu Asn Pro Gly Glu Ile His  
 1790 1795 1800  
 Arg Val Lys Thr Asp Gly Ser Asn Arg Thr Val Phe Ala Pro Leu  
 1805 1810 1815  
 Ser Leu Leu Gly Ser Ser Leu Gly Leu Ala Leu Asp Trp Val Ser  
 1820 1825 1830  
 Arg Asn Ile Tyr Tyr Thr Thr Pro Ala Ser Arg Ser Ile Glu Val  
 1835 1840 1845  
 Leu Thr Leu Lys Gly Asp Thr Arg Tyr Gly Lys Thr Leu Ile Ala  
 1850 1855 1860  
 Asn Asp Gly Thr Pro Leu Gly Val Gly Phe Pro Val Gly Ile Ala  
 1865 1870 1875  
 Val Asp Pro Ala Arg Gly Lys Leu Tyr Trp Ser Asp His Gly Thr  
 1880 1885 1890  
 Asp Ser Gly Val Pro Ala Lys Ile Ala Ser Ala Asn Met Asp Gly  
 1895 1900 1905  
 Thr Ser Leu Lys Ile Leu Phe Thr Gly Asn Leu Gln His Leu Glu  
 1910 1915 1920

## Nonprovisional IP-017.ST25.txt

Val Val Thr Leu Asp Ile Gln Glu Gln Lys Leu Tyr Trp Ala Val  
 1925 1930 1935  
 Thr Ser Arg Gly Val Ile Glu Arg Gly Asn Val Asp Gly Thr Glu  
 1940 1945 1950  
 Arg Met Ile Leu Val His His Leu Ala His Pro Trp Gly Leu Val  
 1955 1960 1965  
 Val Tyr Gly Ser Phe Leu Tyr Tyr Ser Asp Glu Gln Tyr Glu Val  
 1970 1975 1980  
 Ile Glu Arg Val Asp Lys Ser Ser Gly Asn Asn Lys Val Val Leu  
 1985 1990 1995  
 Arg Asp Asn Val Pro Tyr Leu Arg Gly Leu Arg Val Tyr His Arg  
 2000 2005 2010  
 Arg Asn Ala Ala Asp Ser Ser Asn Gly Cys Ser Asn Asn Pro Asn  
 2015 2020 2025  
 Ala Cys Gln Gln Ile Cys Leu Pro Val Pro Gly Gly Met Phe Ser  
 2030 2035 2040  
 Cys Ala Cys Ala Ser Gly Phe Lys Leu Ser Pro Asp Gly Arg Ser  
 2045 2050 2055  
 Cys Ser Pro Tyr Asn Ser Phe Met Val Val Ser Met Leu Pro Ala  
 2060 2065 2070  
 Val Arg Gly Phe Ser Leu Glu Leu Ser Asp His Ser Glu Ala Met  
 2075 2080 2085  
 Val Pro Val Ala Gly Gln Gly Arg Asn Val Leu His Ala Asp Val  
 2090 2095 2100  
 Asp Val Ala Asn Gly Phe Ile Tyr Trp Cys Asp Phe Ser Ser Ser  
 2105 2110 2115  
 Val Arg Ser Ser Asn Gly Ile Arg Arg Ile Lys Pro Asp Gly Ser  
 2120 2125 2130  
 Asn Phe Thr Asn Val Val Thr Tyr Gly Ile Gly Ala Asn Gly Ile  
 2135 2140 2145  
 Arg Gly Val Ala Leu Asp Trp Ala Ala Gly Asn Leu Tyr Phe Thr  
 2150 2155 2160  
 Asn Ala Phe Val Tyr Glu Thr Leu Ile Glu Val Leu Arg Ile Asn  
 2165 2170 2175

## Nonprovisional IP-017.ST25.txt

Thr Thr Tyr Arg Arg Val Leu Leu Lys Val Ser Val Asp Met Pro  
 2180 2185 2190  
 Arg His Ile Ile Val Asp Pro Lys His Arg Tyr Leu Phe Trp Ala  
 2195 2200 2205  
 Asp Tyr Gly Gln Lys Pro Lys Ile Glu Arg Ser Phe Leu Asp Cys  
 2210 2215 2220  
 Thr Asn Arg Thr Val Leu Val Ser Glu Gly Ile Val Thr Pro Arg  
 2225 2230 2235  
 Gly Leu Ala Met Asp His Asp Thr Gly Tyr Ile Tyr Trp Val Asp  
 2240 2245 2250  
 Asp Ser Leu Asp Leu Ile Ala Arg Ile His Leu Asp Gly Gly Glu  
 2255 2260 2265  
 Ser Gln Val Val Arg Tyr Gly Ser Arg Tyr Pro Thr Pro Tyr Gly  
 2270 2275 2280  
 Ile Thr Val Phe Gly Glu Ser Ile Ile Trp Val Asp Arg Asn Leu  
 2285 2290 2295  
 Lys Lys Val Phe Gln Ala Ser Lys Gln Pro Gly Asn Thr Asp Pro  
 2300 2305 2310  
 Pro Val Val Ile Arg Asp Lys Ile Asn Leu Leu Arg Asp Val Thr  
 2315 2320 2325  
 Ile Phe Asp Glu His Ala Gln Pro Leu Ser Pro Ala Glu Leu Asn  
 2330 2335 2340  
 Asn Asn Pro Cys Leu Gln Ser Asn Gly Gly Cys Ser His Phe Cys  
 2345 2350 2355  
 Phe Ala Leu Pro Glu Leu Pro Thr Pro Arg Cys Gly Cys Ala Phe  
 2360 2365 2370  
 Gly Thr Leu Gly Asn Asp Gly Lys Ser Cys Ala Thr Ser Gln Glu  
 2375 2380 2385  
 Asp Phe Leu Ile Tyr Ser Leu Asn Asn Ser Leu Arg Ser Leu His  
 2390 2395 2400  
 Phe Asp Pro Arg Asp His Ser Leu Pro Phe Gln Val Ile Ser Val  
 2405 2410 2415  
 Ala Gly Thr Ala Ile Ala Leu Asp Tyr Asp Arg Arg Asn Asn Arg  
 2420 2425 2430

## Nonprovisional IP-017.ST25.txt

Ile Phe Phe Thr Gln Lys Leu Asn Ser Leu Arg Gly Gln Ile Ser  
 2435 2440 2445  
 Tyr Val Ser Leu Tyr Ser Gly Ser Ser Ser Pro Thr Val Leu Leu  
 2450 2455 2460  
 Ser Asn Ile Gly Val Thr Asp Gly Ile Ala Phe Asp Trp Ile Asn  
 2465 2470 2475  
 Arg Arg Ile Tyr Tyr Ser Asp Phe Ser Asn Gln Thr Ile Asn Ser  
 2480 2485 2490  
 Met Ala Glu Asp Gly Ser Asn Arg Ala Val Ile Ala Arg Val Ser  
 2495 2500 2505  
 Lys Pro Arg Ala Ile Val Leu Asp Pro Cys Arg Gly Tyr Met Tyr  
 2510 2515 2520  
 Trp Thr Asp Trp Gly Thr Asn Ala Lys Ile Glu Arg Ala Thr Leu  
 2525 2530 2535  
 Gly Gly Asn Phe Arg Val Pro Ile Val Asn Thr Ser Leu Val Trp  
 2540 2545 2550  
 Pro Asn Gly Leu Ala Leu Asp Leu Glu Thr Asp Leu Leu Tyr Trp  
 2555 2560 2565  
 Ala Asp Ala Ser Leu Gln Lys Ile Glu Arg Ser Thr Leu Thr Gly  
 2570 2575 2580  
 Thr Asn Arg Glu Val Val Val Ser Thr Ala Phe His Ser Phe Gly  
 2585 2590 2595  
 Leu Thr Val Tyr Gly Gln Tyr Ile Tyr Trp Thr Asp Leu Tyr Thr  
 2600 2605 2610  
 Arg Lys Ile Tyr Arg Ala Asn Lys Tyr Asp Gly Ser Asp Leu Val  
 2615 2620 2625  
 Ala Met Thr Thr Arg Leu Pro Thr Gln Pro Ser Gly Ile Ser Thr  
 2630 2635 2640  
 Val Val Lys Thr Gln Arg Gln Gln Cys Ser Asn Pro Cys Asp Gln  
 2645 2650 2655  
 Phe Asn Gly Gly Cys Ser His Ile Cys Ala Pro Gly Pro Asn Gly  
 2660 2665 2670  
 Ala Glu Cys Gln Cys Pro His Glu Gly Asn Trp Tyr Leu Ala Asn  
 2675 2680 2685



## Nonprovisional IP-017.ST25.txt

Asp Asn Lys Tyr Cys Val Val Asp Thr Gly Thr Arg Cys Asn Gln  
 2690 2695 2700  
 Leu Gln Phe Thr Cys Leu Asn Gly His Cys Ile Asn Gln Asp Trp  
 2705 2710 2715  
 Lys Cys Asp Asn Asp Asn Asp Cys Gly Asp Gly Ser Asp Glu Leu  
 2720 2725 2730  
 Pro Thr Val Cys Ala Phe His Thr Cys Arg Ser Thr Ala Phe Thr  
 2735 2740 2745  
 Cys Gly Asn Gly Arg Cys Val Pro Tyr His Tyr Arg Cys Asp Tyr  
 2750 2755 2760  
 Tyr Asn Asp Cys Gly Asp Asn Ser Asp Glu Ala Gly Cys Leu Phe  
 2765 2770 2775  
 Arg Asn Cys Asn Ser Thr Thr Glu Phe Thr Cys Ser Asn Gly Arg  
 2780 2785 2790  
 Cys Ile Pro Leu Ser Tyr Val Cys Asn Gly Ile Asn Asn Cys His  
 2795 2800 2805  
 Asp Asn Asp Thr Ser Asp Glu Lys Asn Cys Pro Pro His Thr Cys  
 2810 2815 2820  
 Pro Pro Asp Phe Thr Lys Cys Gln Thr Thr Asn Ile Cys Val Pro  
 2825 2830 2835  
 Arg Ala Phe Leu Cys Asp Gly Asp Asn Asp Cys Gly Asp Gly Ser  
 2840 2845 2850  
 Asp Glu Asn Pro Ile Tyr Cys Ala Ser His Thr Cys Arg Ser Asn  
 2855 2860 2865  
 Glu Phe Gln Cys Leu Ser Pro Gln Arg Cys Ile Pro Ser Tyr Trp  
 2870 2875 2880  
 Phe Cys Asp Gly Glu Ala Asp Cys Ala Asp Gly Ser Asp Glu Pro  
 2885 2890 2895  
 Asp Thr Cys Gly His Ser Val Asn Thr Cys Arg Ala Ser Gln Phe  
 2900 2905 2910  
 Gln Cys Asp Asn Gly Arg Cys Ile Ser Gly Asn Trp Val Cys Asp  
 2915 2920 2925  
 Gly Asp Asn Asp Cys Gly Asp Met Ser Asp Glu Asp Gln Arg His  
 2930 2935 2940

## Nonprovisional IP-017.ST25.txt

His Cys Glu Leu Gln Asn Cys Ser Ser Thr Gln Phe Thr Cys Val  
 2945 2950 2955  
 Asn Ser Arg Pro Pro Asn Arg Arg Cys Ile Pro Gln Tyr Trp Val  
 2960 2965 2970  
 Cys Asp Gly Asp Ala Asp Cys Ser Asp Ala Leu Asp Glu Leu Gln  
 2975 2980 2985  
 Asn Cys Thr Met Arg Thr Cys Ser Ala Gly Glu Phe Ser Cys Ala  
 2990 2995 3000  
 Asn Gly Arg Cys Val Arg Gln Ser Phe Arg Cys Asp Arg Arg Asn  
 3005 3010 3015  
 Asp Cys Gly Asp Tyr Ser Asp Glu Arg Gly Cys Ser Tyr Pro Pro  
 3020 3025 3030  
 Cys His Ala Asn Gln Phe Thr Cys Gln Asn Gly Arg Cys Ile Pro  
 3035 3040 3045  
 Arg Phe Phe Val Cys Asp Glu Asp Asn Asp Cys Gly Asp Gly Ser  
 3050 3055 3060  
 Asp Glu Gln Glu His Leu Cys His Thr Pro Glu Pro Thr Cys Pro  
 3065 3070 3075  
 Leu His Gln Phe Arg Cys Asp Asn Gly His Cys Ile Glu Met Gly  
 3080 3085 3090  
 Arg Val Cys Asn His Val Asp Asp Cys Ser Asp Asn Ser Asp Glu  
 3095 3100 3105  
 Lys Gly Cys Gly Ile Asn Glu Cys Leu Asp Ser Ser Ile Ser Arg  
 3110 3115 3120  
 Cys Asp His Asn Cys Thr Asp Thr Ile Thr Ser Phe Tyr Cys Ser  
 3125 3130 3135  
 Cys Leu Pro Gly Tyr Lys Leu Met Ser Asp Lys Arg Ser Cys Val  
 3140 3145 3150  
 Asp Ile Asp Glu Cys Lys Glu Ser Pro Gln Leu Cys Ser Gln Lys  
 3155 3160 3165  
 Cys Glu Asn Val Val Gly Ser Tyr Ile Cys Lys Cys Ala Pro Gly  
 3170 3175 3180  
 Tyr Ile Arg Glu Pro Asp Gly Lys Ser Cys Arg Gln Asn Ser Asn  
 3185 3190 3195

## Nonprovisional IP-017.ST25.txt

Ile Glu Pro Tyr Leu Ile Phe Ser Asn Arg Tyr Tyr Ile Arg Asn  
 3200 3205 3210  
 Leu Thr Thr Asp Gly Ser Ser Tyr Ser Leu Ile Leu Gln Gly Leu  
 3215 3220 3225  
 Gly Asn Val Val Ala Leu Asp Phe Asp Arg Val Glu Lys Arg Leu  
 3230 3235 3240  
 Tyr Trp Ile Asp Ala Glu Lys Gln Ile Ile Glu Arg Met Phe Leu  
 3245 3250 3255  
 Asn Lys Thr Asn Arg Glu Thr Ile Ile Asn His Arg Leu Arg Arg  
 3260 3265 3270  
 Ala Glu Ser Leu Ala Val Asp Trp Val Ser Arg Lys Leu Tyr Trp  
 3275 3280 3285  
 Leu Asp Ala Ile Leu Asp Cys Leu Phe Val Ser Asp Leu Glu Gly  
 3290 3295 3300  
 Arg His Arg Lys Met Ile Ala Gln His Cys Val Asp Ala Asn Asn  
 3305 3310 3315  
 Thr Phe Cys Phe Glu His Pro Arg Gly Ile Val Leu His Pro Gln  
 3320 3325 3330  
 Arg Gly His Val Tyr Trp Ala Asp Trp Gly Val His Ala Tyr Ile  
 3335 3340 3345  
 Gly Arg Ile Gly Met Asp Gly Thr Asn Lys Ser Val Ile Ile Ser  
 3350 3355 3360  
 Thr Lys Ile Glu Trp Pro Asn Ala Ile Thr Ile Asp Tyr Thr Asn  
 3365 3370 3375  
 Asp Leu Leu Tyr Trp Ala Asp Ala His Leu Gly Tyr Ile Glu Phe  
 3380 3385 3390  
 Ser Asp Leu Glu Gly His His Arg His Thr Val Tyr Asp Gly Ser  
 3395 3400 3405  
 Leu Pro His Pro Phe Ala Leu Thr Ile Phe Glu Asp Thr Val Phe  
 3410 3415 3420  
 Trp Thr Asp Trp Asn Thr Arg Thr Val Glu Lys Gly Asn Lys Tyr  
 3425 3430 3435  
 Asp Gly Ser Gly Arg Val Val Leu Val Asn Thr Thr His Lys Pro  
 3440 3445 3450

## Nonprovisional IP-017.ST25.txt

Phe Asp Ile His Val Tyr His Pro Tyr Arg Gln Pro Ile Met Ser  
 3455 3460 3465  
 Asn Pro Cys Gly Thr Asn Asn Gly Gly Cys Ser His Leu Cys Leu  
 3470 3475 3480  
 Ile Lys Ala Gly Gly Arg Gly Phe Thr Cys Ala Cys Pro Asp Asp  
 3485 3490 3495  
 Phe Gln Thr Val Gln Leu Arg Asp Arg Thr Leu Cys Met Pro Met  
 3500 3505 3510  
 Cys Ser Ser Thr Gln Phe Leu Cys Gly Asn Asn Glu Lys Cys Ile  
 3515 3520 3525  
 Pro Ile Trp Trp Lys Cys Asp Gly Gln Lys Asp Cys Ser Asp Gly  
 3530 3535 3540  
 Ser Asp Glu Pro Asp Leu Cys Pro His Arg Phe Cys Arg Leu Gly  
 3545 3550 3555  
 Gln Phe Gln Cys Arg Asp Gly Asn Cys Thr Ser Pro Gln Ala Leu  
 3560 3565 3570  
 Cys Asn Ala Arg Gln Asp Cys Ala Asp Gly Ser Asp Glu Asp Arg  
 3575 3580 3585  
 Val Leu Cys Glu His His Arg Cys Glu Ser Asn Glu Trp Gln Cys  
 3590 3595 3600  
 Ala Asn Lys Arg Cys Ile Pro Gln Ser Trp Gln Cys Asp Ser Val  
 3605 3610 3615  
 Asn Asp Cys Leu Asp Asn Ser Asp Glu Asp Thr Ser His Cys Ala  
 3620 3625 3630  
 Ser Arg Thr Cys Arg Pro Gly Gln Phe Lys Cys Asn Asn Gly Arg  
 3635 3640 3645  
 Cys Ile Pro Gln Ser Trp Lys Cys Asp Val Asp Asn Asp Cys Gly  
 3650 3655 3660  
 Asp Tyr Ser Asp Glu Pro Ile Asp Glu Cys Thr Thr Ala Ala Tyr  
 3665 3670 3675  
 Asn Cys Asp Asn His Thr Glu Phe Ser Cys Lys Thr Asn Tyr Arg  
 3680 3685 3690  
 Cys Ile Pro Gln Trp Ala Val Cys Asn Gly Phe Asp Asp Cys Arg  
 3695 3700 3705

## Nonprovisional IP-017.ST25.txt

Asp Asn Ser Asp Glu Gln Gly Cys Glu Ser Val Pro Cys His Pro  
 3710 3715 3720  
 Ser Gly Asp Phe Arg Cys Ala Asn His His Cys Ile Pro Leu Arg  
 3725 3730 3735  
 Trp Lys Cys Asp Gly Thr Asp Asp Cys Gly Asp Asn Ser Asp Glu  
 3740 3745 3750  
 Glu Asn Cys Val Pro Arg Glu Cys Ser Glu Ser Glu Phe Arg Cys  
 3755 3760 3765  
 Ala Asp Gln Gln Cys Ile Pro Ser Arg Trp Val Cys Asp Gln Glu  
 3770 3775 3780  
 Asn Asp Cys Gly Asp Asn Ser Asp Glu Arg Asp Cys Glu Met Lys  
 3785 3790 3795  
 Thr Cys His Pro Glu His Phe Gln Cys Thr Ser Gly His Cys Val  
 3800 3805 3810  
 Pro Lys Ala Leu Ala Cys Asp Gly Arg Ala Asp Cys Leu Asp Ala  
 3815 3820 3825  
 Ser Asp Glu Ser Ala Cys Pro Thr Arg Phe Pro Asn Gly Thr Tyr  
 3830 3835 3840  
 Cys Pro Ala Ala Met Phe Glu Cys Lys Asn His Val Cys Ile Gln  
 3845 3850 3855  
 Ser Phe Trp Ile Cys Asp Gly Glu Asn Asp Cys Val Asp Gly Ser  
 3860 3865 3870  
 Asp Glu Glu Ile His Leu Cys Phe Asn Ile Pro Cys Glu Ser Pro  
 3875 3880 3885  
 Gln Arg Phe Arg Cys Asp Asn Ser Arg Cys Val Tyr Gly His Gln  
 3890 3895 3900  
 Leu Cys Asn Gly Val Asp Asp Cys Gly Asp Gly Ser Asp Glu Lys  
 3905 3910 3915  
 Glu Glu His Cys Arg Lys Pro Thr His Lys Pro Cys Thr Asp Thr  
 3920 3925 3930  
 Glu Tyr Lys Cys Ser Asn Gly Asn Cys Ile Ser Gln His Tyr Val  
 3935 3940 3945  
 Cys Asp Asn Val Asn Asp Cys Gly Asp Leu Ser Asp Glu Thr Gly  
 3950 3955 3960

## Nonprovisional IP-017.ST25.txt

Cys Asn Leu Gly Asp Asn Arg Thr Cys Ala Glu Asn Ile Cys Glu  
 3965 3970 3975  
 Gln Asn Cys Thr Gln Leu Ser Ser Gly Gly Phe Ile Cys Ser Cys  
 3980 3985 3990  
 Arg Pro Gly Phe Lys Pro Ser Thr Ser Asp Lys Asn Ser Cys Gln  
 3995 4000 4005  
 Asp Ile Asn Glu Cys Glu Glu Phe Gly Ile Cys Pro Gln Ser Cys  
 4010 4015 4020  
 Arg Asn Ser Lys Gly Ser Tyr Glu Cys Phe Cys Val Asp Gly Phe  
 4025 4030 4035  
 Lys Ser Met Ser Thr His Tyr Gly Glu Arg Cys Ala Ala Asp Gly  
 4040 4045 4050  
 Ser Pro Pro Leu Leu Leu Leu Pro Glu Asn Val Arg Ile Arg Lys  
 4055 4060 4065  
 Tyr Asn Thr Ser Ser Glu Lys Phe Ser Glu Tyr Leu Glu Glu Glu  
 4070 4075 4080  
 Glu His Ile Gln Thr Ile Asp Tyr Asp Trp Asp Pro Glu His Ile  
 4085 4090 4095  
 Gly Leu Ser Val Val Tyr Tyr Thr Val Leu Ala Gln Gly Ser Gln  
 4100 4105 4110  
 Phe Gly Ala Ile Lys Arg Ala Tyr Ile Pro Asn Phe Glu Ser Gly  
 4115 4120 4125  
 Ser Asn Asn Pro Ile Arg Glu Val Asp Leu Gly Leu Lys Tyr Leu  
 4130 4135 4140  
 Met Gln Pro Asp Gly Leu Ala Val Asp Trp Val Gly Arg His Ile  
 4145 4150 4155  
 Tyr Trp Ser Asp Ala Lys Ser Gln Arg Ile Glu Val Ala Thr Leu  
 4160 4165 4170  
 Asp Gly Arg Tyr Arg Lys Trp Leu Ile Thr Thr Gln Leu Asp Gln  
 4175 4180 4185  
 Pro Ala Ala Ile Ala Val Asn Pro Lys Leu Gly Leu Met Phe Trp  
 4190 4195 4200  
 Thr Asp Gln Gly Lys Gln Pro Lys Ile Glu Ser Ala Trp Met Asn  
 4205 4210 4215

## Nonprovisional IP-017.ST25.txt

Gly Glu His Arg Ser Val Leu Val Ser Glu Asn Leu Gly Trp Pro  
 4220 4225 4230  
 Asn Gly Leu Ser Ile Asp Tyr Leu Asn Asp Asp Arg Val Tyr Trp  
 4235 4240 4245  
 Ser Asp Ser Lys Glu Asp Val Ile Glu Ala Ile Lys Tyr Asp Gly  
 4250 4255 4260  
 Thr Asp Arg Arg Leu Ile Ile Asn Glu Ala Met Lys Pro Phe Ser  
 4265 4270 4275  
 Leu Asp Ile Phe Glu Asp Lys Leu Tyr Trp Val Ala Lys Glu Lys  
 4280 4285 4290  
 Gly Glu Val Trp Arg Gln Asn Lys Phe Gly Lys Glu Asn Lys Glu  
 4295 4300 4305  
 Lys Val Leu Val Val Asn Pro Trp Leu Thr Gln Val Arg Ile Phe  
 4310 4315 4320  
 His Gln Leu Arg Tyr Asn Gln Ser Val Ser Asn Pro Cys Lys Gln  
 4325 4330 4335  
 Val Cys Ser His Leu Cys Leu Leu Arg Pro Gly Gly Tyr Ser Cys  
 4340 4345 4350  
 Ala Cys Pro Gln Gly Ser Asp Phe Val Thr Gly Ser Thr Val Gln  
 4355 4360 4365  
 Cys Asp Ala Ala Ser Glu Leu Pro Val Thr Met Pro Pro Pro Cys  
 4370 4375 4380  
 Arg Cys Met His Gly Gly Asn Cys Tyr Phe Asp Glu Asn Glu Leu  
 4385 4390 4395  
 Pro Lys Cys Lys Cys Ser Ser Gly Tyr Ser Gly Glu Tyr Cys Glu  
 4400 4405 4410  
 Val Gly Leu Ser Arg Gly Ile Pro Pro Gly Thr Thr Met Ala Val  
 4415 4420 4425  
 Leu Leu Thr Phe Val Ile Val Ile Ile Val Gly Ala Leu Val Leu  
 4430 4435 4440  
 Val Gly Leu Phe His Tyr Arg Lys Thr Gly Ser Leu Leu Pro Thr  
 4445 4450 4455  
 Leu Pro Lys Leu Pro Ser Leu Ser Ser Leu Ala Lys Pro Ser Glu  
 4460 4465 4470

## Nonprovisional IP-017.ST25.txt

Asn Gly Asn Gly Val Thr Phe Arg Ser Gly Ala Asp Val Asn Met  
 4475 4480 4485  
 Asp Ile Gly Val Ser Pro Phe Gly Pro Glu Thr Ile Ile Asp Arg  
 4490 4495 4500  
 Ser Met Ala Met Asn Glu His Phe Val Met Glu Val Gly Lys Gln  
 4505 4510 4515  
 Pro Val Ile Phe Glu Asn Pro Met Tyr Ala Ala Lys Asp Asn Thr  
 4520 4525 4530  
 Ser Lys Val Ala Leu Ala Val Gln Gly Pro Ser Thr Gly Ala Gln  
 4535 4540 4545  
 Val Thr Val Pro Glu Asn Val Glu Asn Gln Asn Tyr Gly Arg Pro  
 4550 4555 4560  
 Ile Asp Pro Ser Glu Ile Val Pro Glu Pro Lys Pro Ala Ser Pro  
 4565 4570 4575  
 Gly Ala Asp Glu Ile Gln Gly Lys Lys Trp Asn Ile Phe Lys Arg  
 4580 4585 4590  
 Lys Pro Lys Gln Thr Thr Asn Phe Glu Asn Pro Ile Tyr Ala Glu  
 4595 4600 4605  
 Met Asp Ser Glu Val Lys Asp Ala Val Ala Val Ala Pro Pro Pro  
 4610 4615 4620  
 Ser Pro Ser Leu Pro Ala Lys Ala Ser Lys Arg Asn Leu Thr Pro  
 4625 4630 4635  
 Gly Tyr Thr Ala Thr Glu Asp Thr Phe Lys Asp Thr Ala Asn Leu  
 4640 4645 4650  
 Val Lys Glu Asp Ser Asp Val  
 4655 4660  
  
 <210> 75  
 <211> 1614  
 <212> PRT  
 <213> MOUSE  
  
 <400> 75  
 Met Glu Thr Ala Pro Thr Arg Ala Pro Pro Pro Pro Pro Pro Pro Leu  
 1 5 10 15  
 Leu Leu Leu Val Leu Tyr Cys Ser Leu Val Pro Ala Ala Ala Ser Pro  
 20 25 30



## Nonprovisional IP-017.ST25.txt

Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala Gly  
 35 40 45  
 Gly Val Lys Leu Glu Ser Thr Ile Val Ala Ser Gly Leu Glu Asp Ala  
 50 55 60  
 Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr Asp  
 65 70 75 80  
 Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly Ala  
 85 90 95  
 Ala Ala Gln Asn Ile Val Ile Ser Gly Leu Val Ser Pro Asp Gly Leu  
 100 105 110  
 Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu Thr  
 115 120 125  
 Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu  
 130 135 140  
 Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala  
 145 150 155 160  
 His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Ala Pro Arg Ile Glu  
 165 170 175  
 Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp  
 180 185 190  
 Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu  
 195 200 205  
 Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His His Ala Asn Leu Asp  
 210 215 220  
 Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe  
 225 230 235 240  
 Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr  
 245 250 255  
 Arg Ser Ile His Ala Cys Asn Lys Trp Thr Gly Glu Gln Arg Lys Glu  
 260 265 270  
 Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln  
 275 280 285  
 Glu Arg Gln Pro Pro Phe His Thr Pro Cys Glu Glu Asp Asn Gly Gly  
 290 295 300

## Nonprovisional IP-017.ST25.txt

Cys Ser His Leu Cys Leu Leu Ser Pro Arg Glu Pro Phe Tyr Ser Cys  
 305 310 315 320  
 Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Lys Thr Cys Lys  
 325 330 335  
 Thr Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg  
 340 345 350  
 Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val  
 355 360 365  
 Gly Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly  
 370 375 380  
 Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr  
 385 390 395 400  
 Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp  
 405 410 415  
 Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr  
 420 425 430  
 Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser  
 435 440 445  
 Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Val  
 450 455 460  
 Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn  
 465 470 475 480  
 Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Arg Asp Arg His Val Leu  
 485 490 495  
 Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln  
 500 505 510  
 Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val  
 515 520 525  
 Ile Asn Ile Asp Gly Thr Lys Arg Lys Thr Leu Leu Glu Asp Lys Leu  
 530 535 540  
 Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr  
 545 550 555 560  
 Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser  
 565 570 575

## Nonprovisional IP-017.ST25.txt

Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala  
 580 585 590  
 Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Gly Asn  
 595 600 605  
 Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro Arg Ala Thr Lys Cys  
 610 615 620  
 Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile  
 625 630 635 640  
 Ile Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Thr Ile His Arg  
 645 650 655  
 Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly  
 660 665 670  
 Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile  
 675 680 685  
 Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn  
 690 695 700  
 Gly Ser Ser Val Glu His Val Ile Glu Phe Gly Leu Asp Tyr Pro Glu  
 705 710 715 720  
 Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr  
 725 730 735  
 Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln  
 740 745 750  
 Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp  
 755 760 765  
 Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg  
 770 775 780  
 Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp  
 785 790 795 800  
 Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg  
 805 810 815  
 Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met  
 820 825 830  
 Leu Gly Gln Glu Arg Met Val Ile Ala Asp Asp Leu Pro Tyr Pro Phe  
 835 840 845

## Nonprovisional IP-017.ST25.txt

Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu  
 850 855 860

His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu  
 865 870 875 880

Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser  
 885 890 895

Ser Arg Gln Asp Gly Leu Asn Asp Cys Val His Ser Asn Gly Gln Cys  
 900 905 910

Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala  
 915 920 925

Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Ser  
 930 935 940

Thr Phe Leu Leu Phe Ser Gln Lys Phe Ala Ile Ser Arg Met Ile Pro  
 945 950 955 960

Asp Asp Gln Leu Ser Pro Asp Leu Val Leu Pro Leu His Gly Leu Arg  
 965 970 975

Asn Val Lys Ala Ile Asn Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp  
 980 985 990

Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr Gln  
 995 1000 1005

Pro Ser Met Leu Thr Ser Pro Ser Gln Ser Leu Ser Pro Asp Arg  
 1010 1015 1020

Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe  
 1025 1030 1035

Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Asp  
 1040 1045 1050

Gly Asp Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys Pro  
 1055 1060 1065

Arg Ala Ile Ala Val Asn Ala Glu Arg Gly Tyr Met Tyr Phe Thr  
 1070 1075 1080

Asn Met Gln Asp His Ala Ala Lys Ile Glu Arg Ala Ser Leu Asp  
 1085 1090 1095

Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg Pro  
 1100 1105 1110

## Nonprovisional IP-017.ST25.txt

Val Ala Leu Val Val Asp Asn Ala Leu Gly Lys Leu Phe Trp Val  
 1115 1120 1125  
 Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly Ala  
 1130 1135 1140  
 Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Val Gly  
 1145 1150 1155  
 Leu Thr Val Leu Gly Arg His Leu Tyr Trp Ile Asp Arg Gln Gln  
 1160 1165 1170  
 Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg Thr  
 1175 1180 1185  
 Arg Val Gln Gly Arg Val Thr His Leu Thr Gly Ile His Ala Val  
 1190 1195 1200  
 Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala Arg  
 1205 1210 1215  
 Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp Gly  
 1220 1225 1230  
 Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln Asn  
 1235 1240 1245  
 Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln Phe  
 1250 1255 1260  
 Ala Cys Thr Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp Arg  
 1265 1270 1275  
 Cys Asp Gly Phe Pro Glu Cys Ala Asp Gln Ser Asp Glu Glu Gly  
 1280 1285 1290  
 Cys Pro Val Cys Ser Ala Ser Gln Phe Pro Cys Ala Arg Gly Gln  
 1295 1300 1305  
 Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys Gln  
 1310 1315 1320  
 Asp Arg Ser Asp Glu Ala Asn Cys Asp Ala Val Cys Leu Pro Asn  
 1325 1330 1335  
 Gln Phe Arg Cys Thr Ser Gly Gln Cys Val Leu Ile Lys Gln Gln  
 1340 1345 1350  
 Cys Asp Ser Phe Pro Asp Cys Ala Asp Gly Ser Asp Glu Leu Met  
 1355 1360 1365

Nonprovisional IP-017.ST25.txt

Cys Glu Ile Asn Lys Pro Pro Ser Asp Asp Ile Pro Ala His Ser  
 1370 1375 1380  
 Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe Val  
 1385 1390 1395  
 Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Met Cys Gln Arg  
 1400 1405 1410  
 Tyr Thr Gly Ala Ser Gly Pro Phe Pro His Glu Tyr Val Gly Gly  
 1415 1420 1425  
 Ala Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser Gln  
 1430 1435 1440  
 His Gly Pro Phe Pro Gly Ile Pro Cys Ser Lys Ser Val Met Ser  
 1445 1450 1455  
 Ser Met Ser Leu Val Gly Gly Arg Gly Ser Val Pro Leu Tyr Asp  
 1460 1465 1470  
 Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser Thr  
 1475 1480 1485  
 Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro  
 1490 1495 1500  
 Ala Thr Asp Pro Ser Leu Tyr Asn Val Asp Val Phe Tyr Ser Ser  
 1505 1510 1515  
 Gly Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Val Ile Arg  
 1520 1525 1530  
 Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp  
 1535 1540 1545  
 Ser Asp Tyr Ser Ile Ser Arg Trp Lys Ser Ser Lys Tyr Tyr Leu  
 1550 1555 1560  
 Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro  
 1565 1570 1575  
 His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro  
 1580 1585 1590  
 Gly Thr Glu Arg Ser Tyr Cys His Leu Phe Pro Pro Pro Pro Ser  
 1595 1600 1605  
 Pro Cys Thr Asp Ser Ser  
 1610

## Nonprovisional IP-017.ST25.txt

<210> 76  
 <211> 770  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 76

Met Glu Lys Arg Ala Ala Ala Gly Leu Glu Gly Ala Pro Gly Ala Arg  
 1 5 10 15

Ala Gln Leu Ala Val Val Cys Leu Val Asn Ile Phe Leu Thr Gly Arg  
 20 25 30

Leu Ser Ser Ala Val Pro Ala Leu Ala Ala Cys Ser Gly Lys Leu Glu  
 35 40 45

Gln His Thr Glu Arg Arg Gly Val Ile Tyr Ser Pro Ala Trp Pro Leu  
 50 55 60

Asn Tyr Pro Pro Gly Thr Asn Cys Ser Trp Tyr Ile Gln Gly Asp Arg  
 65 70 75 80

Gly Asp Met Ile Thr Ile Ser Phe Arg Asn Phe Asp Val Glu Glu Ser  
 85 90 95

His Gln Cys Ser Leu Asp Trp Leu Leu Leu Gly Pro Ala Ala Pro Pro  
 100 105 110

Arg Gln Glu Ala Phe Arg Leu Cys Gly Ser Ala Ile Pro Pro Ala Phe  
 115 120 125

Ile Ser Ala Arg Asp His Val Trp Ile Phe Phe His Ser Asp Ala Ser  
 130 135 140

Ser Ser Gly Gln Ala Gln Gly Phe Arg Leu Ser Tyr Ile Arg Gly Lys  
 145 150 155 160

Leu Gly Gln Ala Ser Cys Gln Ala Asp Glu Phe Arg Cys Asp Asn Gly  
 165 170 175

Lys Cys Leu Pro Gly Pro Trp Gln Cys Asn Thr Val Asp Glu Cys Gly  
 180 185 190

Asp Gly Ser Asp Glu Gly Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro  
 195 200 205

Gly Ser Leu Cys Pro Gly Gly Thr Phe Pro Cys Ser Gly Ala Arg Ser  
 210 215 220

Thr Arg Cys Leu Pro Val Glu Arg Arg Cys Asp Gly Leu Gln Asp Cys  
 225 230 235 240

Gly Asp Gly Ser Asp Glu Ala Gly Cys Pro Asp Leu Ala Cys Gly Arg  
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Nonprovisional IP-017.ST25.txt  
 245 250 255

Arg Leu Gly Ser Phe Tyr Gly Ser Phe Ala Ser Pro Asp Leu Phe Gly  
 260 265 270

Ala Ala Arg Gly Pro Ser Asp Leu His Cys Thr Trp Leu Val Asp Thr  
 275 280 285

Gln Asp Ser Arg Arg Val Leu Leu Gln Leu Glu Leu Arg Leu Gly Tyr  
 290 295 300

Asp Asp Tyr Val Gln Val Tyr Glu Gly Leu Gly Glu Arg Gly Asp Arg  
 305 310 315 320

Leu Leu Gln Thr Leu Ser Tyr Arg Ser Asn His Arg Pro Val Ser Leu  
 325 330 335

Glu Ala Ala Gln Gly Arg Leu Thr Val Ala Tyr His Ala Arg Ala Arg  
 340 345 350

Ser Ala Gly His Gly Phe Asn Ala Thr Tyr Gln Val Lys Gly Tyr Cys  
 355 360 365

Leu Pro Trp Glu Gln Pro Cys Gly Ser Ser Ser Asp Ser Asp Gly Gly  
 370 375 380

Ser Leu Gly Asp Gln Gly Cys Phe Ser Glu Pro Gln Arg Cys Asp Gly  
 385 390 400

Trp Trp His Cys Ala Ser Gly Arg Asp Glu Gln Gly Cys Pro Ala Cys  
 405 410 415

Pro Pro Asp Gln Tyr Pro Cys Glu Gly Gly Ser Gly Leu Cys Tyr Thr  
 420 425 430

Pro Ala Asp Arg Cys Asn Asn Gln Lys Ser Cys Pro Asp Gly Ala Asp  
 435 440 445

Glu Lys Asn Cys Phe Ser Cys Gln Pro Gly Thr Phe His Cys Gly Thr  
 450 455 460

Asn Leu Cys Ile Phe Glu Thr Trp Arg Cys Asp Gly Gln Glu Asp Cys  
 465 470 475 480

Gln Asp Gly Ser Asp Glu His Gly Cys Leu Ala Ala Val Pro Arg Lys  
 485 490 495

Val Ile Thr Ala Ala Leu Ile Gly Ser Leu Val Cys Gly Leu Leu Leu  
 500 505 510

Val Ile Ala Leu Gly Cys Ala Phe Lys Leu Tyr Ser Leu Arg Thr Gln  
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Nonprovisional IP-017.ST25.txt

515

520

525

Glu Tyr Arg Ala Phe Glu Thr Gln Met Thr Arg Leu Glu Ala Glu Phe  
 530 535 540

Val Arg Arg Glu Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly  
 545 550 555 560

Leu Ile Pro Pro Val Glu Asp Phe Pro Val Tyr Ser Ala Ser Gln Ala  
 565 570 575

Ser Val Leu Gln Asn Leu Arg Thr Ala Met Arg Arg Gln Met Arg Arg  
 580 585 590

His Ala Ser Arg Arg Gly Pro Ser Arg Arg Arg Leu Gly Arg Leu Trp  
 595 600 605

Asn Arg Leu Phe His Arg Pro Arg Ala Pro Arg Gly Gln Ile Pro Leu  
 610 615 620

Leu Thr Ala Ala Arg Pro Ser Gln Thr Val Leu Gly Asp Gly Phe Leu  
 625 630 635 640

Gln Pro Ala Pro Gly Ala Ala Pro Asp Pro Pro Ala Pro Leu Met Asp  
 645 650 655

Thr Gly Ser Thr Arg Ala Ala Gly Asp Arg Pro Pro Ser Ala Pro Gly  
 660 665 670

Arg Ala Pro Glu Val Gly Pro Ser Gly Pro Pro Leu Pro Ser Gly Leu  
 675 680 685

Arg Asp Pro Glu Cys Arg Pro Val Asp Lys Asp Arg Lys Val Cys Arg  
 690 695 700

Glu Pro Leu Val Asp Gly Pro Ala Pro Ala Asp Ala Pro Arg Glu Pro  
 705 710 715 720

Cys Ser Ala Gln Asp Pro His Pro Gln Val Ser Thr Ala Ser Ser Thr  
 725 730 735

Leu Gly Pro His Ser Pro Glu Pro Leu Gly Val Cys Arg Asn Pro Pro  
 740 745 750

Pro Pro Cys Ser Pro Met Leu Glu Ala Ser Asp Asp Glu Ala Leu Leu  
 755 760 765

Val Cys  
 770

&lt;210&gt; 77

## Nonprovisional IP-017.ST25.txt

<211> 770  
 <212> PRT  
 <213> RAT

<400> 77

Met Glu Lys Arg Ala Ala Ala Gly Pro Glu Gly Ala Pro Gly Ala Arg  
 1 5 10 15

Ala Pro Leu Ala Val Val Cys Leu Val Asn Leu Phe Leu Thr Gly Arg  
 20 25 30

Leu Ser Ser Ala Val Pro Ala Leu Ala Ala Cys Ser Gly Lys Leu Glu  
 35 40 45

Gln His Thr Glu Arg Arg Gly Val Ile Tyr Ser Pro Ala Trp Pro Leu  
 50 55 60

Asn Tyr Pro Pro Gly Thr Asn Cys Ser Trp Tyr Ile Gln Gly Asp Arg  
 65 70 75 80

Gly Asp Met Ile Thr Ile Ser Phe Arg Asn Phe Asp Val Glu Glu Ser  
 85 90 95

His Gln Cys Ser Leu Asp Trp Leu Leu Leu Gly Pro Ala Ala Pro Pro  
 100 105 110

Arg Gln Glu Ala Phe Arg Leu Cys Gly Ser Ala Ile Pro Pro Ala Phe  
 115 120 125

Ile Ser Ala Arg Asp His Val Trp Ile Phe Phe His Ser Asp Ala Ser  
 130 135 140

Ser Ser Gly Gln Ala Gln Gly Phe Arg Leu Ser Tyr Ile Arg Gly Lys  
 145 150 155 160

Leu Gly Gln Ala Ser Cys Gln Thr Asp Glu Phe Arg Cys Asp Asn Gly  
 165 170 175

Lys Cys Leu Pro Gly Pro Trp Gln Cys Asn Met Val Asp Glu Cys Gly  
 180 185 190

Asp Gly Ser Asp Glu Gly Asn Cys Ser Ala Pro Ala Ser Glu Pro Pro  
 195 200 205

Gly Ser Leu Cys Pro Gly Gly Thr Phe Pro Cys Ser Gly Ala Arg Ser  
 210 215 220

Thr Arg Cys Leu Pro Val Glu Arg Arg Cys Asp Gly Thr Gln Asp Cys  
 225 230 235 240

Gly Asp Gly Ser Asp Glu Ala Gly Cys Pro Asp Leu Ala Cys Gly Arg  
 245 250 255

## Nonprovisional IP-017.ST25.txt

Arg Leu Gly Ser Phe Tyr Gly Ser Phe Ala Ser Pro Asp Leu Phe Gly  
 260 265 270  
 Ala Ala Arg Gly Pro Ser Asp Leu His Cys Thr Trp Leu Val Asp Thr  
 275 280 285  
 Gln Asp Pro Arg Arg Val Leu Leu Gln Leu Glu Leu Arg Leu Gly Tyr  
 290 295 300  
 Asp Asp Tyr Val Gln Val Tyr Glu Gly Leu Gly Glu Arg Gly Asp Arg  
 305 310 315 320  
 Leu Leu Gln Thr Leu Ser Tyr Arg Ser Asn His Arg Pro Val Ser Leu  
 325 330 335  
 Glu Ala Ala Gln Gly Arg Leu Thr Val Ala Tyr His Ala Arg Ala Arg  
 340 345 350  
 Ser Ala Gly His Gly Phe Asn Ala Thr Tyr Gln Val Lys Gly Tyr Cys  
 355 360 365  
 Leu Pro Trp Glu Gln Pro Cys Gly Ser Ser Ser Glu Gly Asp Asp Gly  
 370 375 380  
 Ser Thr Gly Glu Gln Gly Cys Phe Ser Glu Pro Gln Arg Cys Asp Gly  
 385 390 395 400  
 Trp Trp His Cys Ala Ser Gly Arg Asp Glu Gln Gly Cys Pro Ala Cys  
 405 410 415  
 Pro Pro Asp Gln Tyr Pro Cys Glu Gly Gly Ser Gly Leu Cys Tyr Ala  
 420 425 430  
 Pro Ala Asp Arg Cys Asn Asn Gln Lys Ser Cys Pro Asp Gly Ala Asp  
 435 440 445  
 Glu Lys Asn Cys Phe Ser Cys Gln Pro Gly Thr Phe His Cys Gly Thr  
 450 455 460  
 Asn Leu Cys Ile Phe Glu Thr Trp Arg Cys Asp Gly Gln Glu Asp Cys  
 465 470 475 480  
 Gln Asp Gly Ser Asp Glu His Gly Cys Leu Ala Ala Val Pro Arg Lys  
 485 490 495  
 Val Ile Thr Ala Ala Leu Ile Gly Ser Leu Val Cys Gly Leu Leu Leu  
 500 505 510  
 Val Ile Ala Leu Gly Cys Ala Phe Lys Leu Tyr Ser Leu Arg Thr Gln  
 515 520 525

## Nonprovisional IP-017.ST25.txt

Glu Tyr Arg Ala Phe Glu Thr Gln Met Thr Arg Leu Glu Ala Glu Phe  
 530 535 540  
 Val Arg Arg Glu Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly  
 545 550 555 560  
 Leu Ile Pro Pro Val Glu Asp Phe Pro Val Tyr Ser Ala Ser Gln Ala  
 565 570 575  
 Ser Val Leu Gln Asn Leu Arg Thr Ala Met Arg Arg Gln Met Arg Arg  
 580 585 590  
 His Ala Ser Arg Arg Gly Pro Ser Arg Arg Arg Leu Gly Arg Leu Trp  
 595 600 605  
 Asn Arg Leu Phe His Arg Pro Arg Ala Pro Arg Gly Gln Ile Pro Leu  
 610 615 620  
 Leu Thr Ala Ala Arg Thr Ser Gln Thr Val Leu Gly Asp Gly Leu Leu  
 625 630 635 640  
 Gln Ala Ala Pro Gly Pro Val Pro Asp Pro Pro Val Pro Asn Thr Asp  
 645 650 655  
 Thr Gly Ser Pro Arg Glu Ala Gly Asp Gly Pro Pro Ser Gly Ser Gly  
 660 665 670  
 His Ala Pro Glu Val Gly Pro Ser Val Pro Pro Pro Pro Leu Asn Leu  
 675 680 685  
 Arg Asp Pro Glu Tyr Arg Pro Glu Asp Lys Glu Arg Lys Ala Cys Val  
 690 695 700  
 Asp Pro Leu Glu Asp Ser Pro Ala Pro Val Asp Thr Pro Pro Glu Pro  
 705 710 715 720  
 Cys Leu Ala Gln Asp Pro His Pro Gln Thr Pro Thr Ala Ser Gly Ile  
 725 730 735  
 Gln Asp Pro His Ser Ala Glu Pro Leu Gly Val Cys Arg Ser Pro Pro  
 740 745 750  
 Pro Thr Cys Ser Pro Ile Leu Glu Ala Ser Asp Asp Glu Ala Leu Leu  
 755 760 765  
 Val Cys  
 770

<210> 78  
 <211> 1113

## Nonprovisional IP-017.ST25.txt

<212> PRT  
 <213> MOUSE

<400> 78

Met Gly Arg Val Ser Phe Ser Val Arg Val Ser Ser Val Arg Arg Ala  
 1 5 10 15

Arg Cys Ser Cys Pro Gly Arg Cys Tyr Leu Ser Cys Arg Val Pro Pro  
 20 25 30

Thr Thr Ala Leu Arg Ala Leu Asn Gly Leu Gly Cys Ala Gly Val Pro  
 35 40 45

Gly Glu Thr Ala Gly Gly Ala Val Gly Pro Gly Pro Leu Gly Thr Arg  
 50 55 60

Gly Phe Leu Ser Gly Ser Lys Phe Gln Ala Pro Gly Ser Trp Lys Asp  
 65 70 75 80

Cys Phe Gly Ala Pro Pro Ala Pro Asp Val Leu Arg Ala Asp Arg Ser  
 85 90 95

Val Gly Glu Gly Cys Pro Gln Lys Leu Val Thr Ala Asn Leu Leu Arg  
 100 105 110

Phe Leu Leu Leu Val Leu Ile Pro Cys Ile Cys Ala Leu Ile Val Leu  
 115 120 125

Leu Ala Ile Leu Leu Ser Phe Val Gly Thr Leu Lys Arg Val Tyr Phe  
 130 135 140

Lys Ser Asn Asp Ser Glu Pro Leu Val Thr Asp Gly Glu Ala Arg Val  
 145 150 155 160

Pro Gly Val Ile Pro Val Asn Thr Val Tyr Tyr Glu Asn Thr Gly Ala  
 165 170 175

Pro Ser Leu Pro Pro Ser Gln Ser Thr Pro Ala Trp Thr Pro Arg Ala  
 180 185 190

Pro Ser Pro Glu Asp Gln Ser His Arg Asn Thr Ser Thr Cys Met Asn  
 195 200 205

Ile Thr His Ser Gln Cys Gln Ile Leu Pro Tyr His Ser Thr Leu Ala  
 210 215 220

Pro Leu Leu Pro Ile Val Lys Asn Met Asp Met Glu Lys Phe Leu Lys  
 225 230 235 240

Phe Phe Thr Tyr Leu His Arg Leu Ser Cys Tyr Gln His Ile Leu Leu  
 245 250 255

## Nonprovisional IP-017.ST25.txt

Phe Gly Cys Ser<sub>260</sub> Leu Ala Phe Pro Glu<sub>265</sub> Cys Val Val Asp Gly<sub>270</sub> Asp Asp  
 Arg His Gly<sub>275</sub> Leu Leu Pro Cys Arg<sub>280</sub> Ser Phe Cys Glu Ala<sub>285</sub> Ala Lys Glu  
 Gly Cys<sub>290</sub> Glu Ser Val Leu Gly<sub>295</sub> Met Val Asn Ser Ser<sub>300</sub> Trp Pro Asp Ser  
 Leu Arg Cys Ser Gln Phe<sub>310</sub> Arg Asp His Thr Glu<sub>315</sub> Thr Asn Ser Ser Val<sub>320</sub>  
 Arg Lys Ser Cys Phe<sub>325</sub> Ser Leu Gln Gln Glu<sub>330</sub> His Gly Lys Gln Ser<sub>335</sub> Leu  
 Cys Gly Gly Gly<sub>340</sub> Glu Ser Phe Leu Cys<sub>345</sub> Thr Ser Gly Leu Cys<sub>350</sub> Val Pro  
 Lys Lys Leu<sub>355</sub> Gln Cys Asn Gly Tyr<sub>360</sub> Asn Asp Cys Asp Asp<sub>365</sub> Trp Ser Asp  
 Glu Ala His Cys Asn Cys Ser<sub>375</sub> Lys Asp Leu Phe His<sub>380</sub> Cys Gly Thr Gly  
 Lys Cys Leu His Tyr Ser<sub>390</sub> Leu Leu Cys Asp Gly<sub>395</sub> Tyr Asp Asp Cys Gly<sub>400</sub>  
 Asp Pro Ser Asp Glu<sub>405</sub> Gln Asn Cys Asp Cys<sub>410</sub> Asn Leu Thr Lys Glu<sub>415</sub> His  
 Arg Cys Gly Asp<sub>420</sub> Gly Arg Cys Ile Ala<sub>425</sub> Ala Glu Trp Val Cys<sub>430</sub> Asp Gly  
 Asp His Asp<sub>435</sub> Cys Val Asp Lys Ser<sub>440</sub> Asp Glu Val Asn Cys<sub>445</sub> Ser Cys His  
 Ser Gln Gly Leu Val Glu Cys<sub>455</sub> Thr Ser Gly Gln Cys<sub>460</sub> Ile Pro Ser Thr  
 Phe Gln Cys Asp Gly Asp<sub>470</sub> Glu Asp Cys Lys Asp<sub>475</sub> Gly Ser Asp Glu Glu<sub>480</sub>  
 Asn Cys Ser Asp Ser<sub>485</sub> Gln Thr Pro Cys Pro<sub>490</sub> Glu Gly Glu Gln Gly<sub>495</sub> Cys  
 Phe Gly Ser Ser<sub>500</sub> Cys Val Glu Ser Cys<sub>505</sub> Ala Gly Ser Ser Leu<sub>510</sub> Cys Asp  
 Ser Asp Ser<sub>515</sub> Ser Leu Ser Asn Cys<sub>520</sub> Ser Gln Cys Glu Pro<sub>525</sub> Ile Thr Leu

## Nonprovisional IP-017.ST25.txt

Glu Leu Cys Met Asn Leu Leu Tyr Asn His Thr His Tyr Pro Asn Tyr  
 530 535 540  
 Leu Gly His Arg Thr Gln Lys Glu Ala Ser Ile Ser Trp Glu Ser Ser  
 545 550 555 560  
 Leu Phe Pro Ala Leu Val Gln Thr Asn Cys Tyr Lys Tyr Leu Met Phe  
 565 570 575  
 Phe Ala Cys Thr Ile Leu Val Pro Lys Cys Asp Val Asn Thr Gly Gln  
 580 585 590  
 Arg Ile Pro Pro Cys Arg Leu Leu Cys Glu His Ser Lys Glu Arg Cys  
 595 600 605  
 Glu Ser Val Leu Gly Ile Val Gly Leu Gln Trp Pro Glu Asp Thr Asp  
 610 615 620  
 Cys Asn Gln Phe Pro Glu Glu Ser Ser Asp Asn Gln Thr Cys Leu Leu  
 625 630 635 640  
 Pro Asn Glu Asp Val Glu Glu Cys Ser Pro Ser His Phe Lys Cys Arg  
 645 650 655  
 Ser Gly Arg Cys Val Leu Gly Ser Arg Arg Cys Asp Gly Gln Ala Asp  
 660 665 670  
 Cys Asp Asp Asp Ser Asp Glu Glu Asn Cys Gly Cys Lys Glu Arg Ala  
 675 680 685  
 Leu Trp Glu Cys Pro Phe Asn Lys Gln Cys Leu Lys His Thr Leu Ile  
 690 695 700  
 Cys Asp Gly Phe Pro Asp Cys Pro Asp Ser Met Asp Glu Lys Asn Cys  
 705 710 715 720  
 Ser Phe Cys Gln Asp Asn Glu Leu Glu Cys Ala Asn His Glu Cys Val  
 725 730 735  
 Pro Arg Asp Leu Trp Cys Asp Gly Trp Val Asp Cys Ser Asp Ser Ser  
 740 745 750  
 Asp Glu Trp Gly Cys Val Thr Leu Ser Lys Asn Gly Asn Ser Ser Ser  
 755 760 765  
 Leu Leu Thr Val His Lys Ser Ala Lys Glu His His Val Cys Ala Asp  
 770 775 780  
 Gly Trp Arg Glu Thr Leu Ser Gln Leu Ala Cys Lys Gln Met Gly Leu  
 785 790 795 800

## Nonprovisional IP-017.ST25.txt

Gly Glu Pro Ser Val Thr Lys Leu Ile Pro Gly Gln Glu Gly Gln Gln  
 805 810 815  
 Trp Leu Arg Leu Tyr Pro Asn Trp Glu Asn Leu Asn Gly Ser Thr Leu  
 820 825 830  
 Gln Glu Leu Leu Val Tyr Arg His Ser Cys Pro Ser Arg Ser Glu Ile  
 835 840 845  
 Ser Leu Leu Cys Ser Lys Gln Asp Cys Gly Arg Arg Pro Ala Ala Arg  
 850 855 860  
 Met Asn Lys Arg Ile Leu Gly Gly Arg Thr Ser Arg Pro Gly Arg Trp  
 865 870 875 880  
 Pro Trp Gln Cys Ser Leu Gln Ser Glu Pro Ser Gly His Ile Cys Gly  
 885 890 895  
 Cys Val Leu Ile Ala Lys Lys Trp Val Leu Thr Val Ala His Cys Phe  
 900 905 910  
 Glu Gly Arg Glu Asp Ala Asp Val Trp Lys Val Val Phe Gly Ile Asn  
 915 920 925  
 Asn Leu Asp His Pro Ser Gly Phe Met Gln Thr Arg Phe Val Lys Thr  
 930 935 940  
 Ile Leu Leu His Pro Arg Tyr Ser Arg Ala Val Val Asp Tyr Asp Ile  
 945 950 955 960  
 Ser Val Val Glu Leu Ser Asp Asp Ile Asn Glu Thr Ser Tyr Val Arg  
 965 970 975  
 Pro Val Cys Leu Pro Ser Pro Glu Glu Tyr Leu Glu Pro Asp Thr Tyr  
 980 985 990  
 Cys Tyr Ile Thr Gly Trp Gly His Met Gly Asn Lys Met Pro Phe Lys  
 995 1000 1005  
 Leu Gln Glu Gly Glu Val Arg Ile Ile Pro Leu Glu Gln Cys Gln  
 1010 1015 1020  
 Ser Tyr Phe Asp Met Lys Thr Ile Thr Asn Arg Met Ile Cys Ala  
 1025 1030 1035  
 Gly Tyr Glu Ser Gly Thr Val Asp Ser Cys Met Gly Asp Ser Gly  
 1040 1045 1050  
 Gly Pro Leu Val Cys Glu Arg Pro Gly Gly Gln Trp Thr Leu Phe  
 1055 1060 1065



## Nonprovisional IP-017.ST25.txt

Gly Leu Thr Ser Trp Gly Ser Val Cys Phe Ser Lys Val Leu Gly  
1070 1075 1080

Pro Gly Val Tyr Ser Asn Val Ser Tyr Phe Val Gly Trp Ile Glu  
1085 1090 1095

Arg Gln Ile Tyr Ile Gln Thr Phe Leu Gln Lys Lys Ser Gln Gly  
1100 1105 1110

<210> 79  
<211> 859  
<212> PRT  
<213> HOMO SAPIENS

<400> 79

Met Asn Ser Phe Leu Ile Phe Ala Arg Arg Ile Asp Ile Arg Met Val  
1 5 10 15

Ser Leu Asp Ile Pro Tyr Phe Ala Asp Val Val Val Pro Ile Asn Ile  
20 25 30

Thr Met Lys Asn Thr Ile Ala Ile Gly Val Asp Pro Gln Glu Gly Lys  
35 40 45

Val Tyr Trp Ser Asp Ser Thr Leu His Arg Ile Ser Arg Ala Asn Leu  
50 55 60

Asp Gly Ser Gln His Glu Asp Ile Ile Thr Thr Gly Leu Gln Thr Thr  
65 70 75 80

Asp Gly Leu Ala Val Asp Ala Ile Gly Arg Lys Val Tyr Trp Thr Asp  
85 90 95

Thr Gly Thr Asn Arg Ile Glu Val Gly Asn Leu Asp Gly Ser Met Arg  
100 105 110

Lys Val Leu Val Trp Gln Asn Leu Asp Ser Pro Arg Ala Ile Val Leu  
115 120 125

Tyr His Glu Met Gly Phe Met Tyr Trp Thr Asp Trp Gly Glu Asn Ala  
130 135 140

Lys Leu Glu Arg Ser Gly Met Asp Gly Ser Asp Arg Ala Val Leu Ile  
145 150 155 160

Asn Asn Asn Leu Gly Trp Pro Asn Gly Leu Thr Val Asp Lys Ala Ser  
165 170 175

Ser Gln Leu Leu Trp Ala Asp Ala His Thr Glu Arg Ile Glu Ala Ala  
180 185 190

## Nonprovisional IP-017.ST25.txt

Asp Leu Asn Gly Ala Asn Arg His Thr Leu Val Ser Pro Val Gln His  
 195 200 205  
 Pro Tyr Gly Leu Thr Leu Leu Asp Ser Tyr Ile Tyr Trp Thr Asp Trp  
 210 215 220  
 Gln Thr Arg Ser Ile His Arg Ala Asp Lys Gly Thr Gly Ser Asn Val  
 225 230 235 240  
 Ile Leu Val Arg Ser Asn Leu Pro Gly Leu Met Asp Met Gln Ala Val  
 245 250 255  
 Asp Arg Ala Gln Pro Leu Gly Phe Asn Lys Cys Gly Ser Arg Asn Gly  
 260 265 270  
 Gly Cys Ser His Leu Cys Leu Pro Arg Pro Ser Gly Phe Ser Cys Ala  
 275 285  
 Cys Pro Thr Gly Ile Gln Leu Lys Gly Asp Gly Lys Thr Cys Asp Pro  
 290 295 300  
 Ser Pro Glu Thr Tyr Leu Leu Phe Ser Ser Arg Gly Ser Ile Arg Arg  
 305 310 315 320  
 Ile Ser Leu Asp Thr Ser Asp His Thr Asp Val His Val Pro Val Pro  
 325 330 335  
 Glu Leu Asn Asn Val Ile Ser Leu Asp Tyr Asp Ser Val Asp Gly Lys  
 340 345 350  
 Val Tyr Tyr Thr Asp Val Phe Leu Asp Val Ile Arg Arg Ala Asp Leu  
 355 360 365  
 Asn Gly Ser Asn Met Glu Thr Val Ile Gly Arg Gly Leu Lys Thr Thr  
 370 375 380  
 Asp Gly Leu Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr Asp  
 385 390 395 400  
 Thr Gly Arg Asn Thr Ile Glu Ala Ser Arg Leu Asp Gly Ser Cys Arg  
 405 410 415  
 Lys Val Leu Ile Asn Asn Ser Leu Asp Glu Pro Arg Ala Ile Ala Val  
 420 425 430  
 Phe Pro Arg Lys Gly Tyr Leu Phe Trp Thr Asp Trp Gly His Ile Ala  
 435 440 445  
 Lys Ile Glu Arg Ala Asn Leu Asp Gly Ser Glu Arg Lys Val Leu Ile  
 450 455 460

## Nonprovisional IP-017.ST25.txt

Asn Thr Asp Leu Gly Trp Pro Asn Gly Leu Thr Leu Asp Tyr Asp Thr  
 465 470 475 480  
 Arg Arg Ile Tyr Trp Val Asp Ala His Leu Asp Arg Ile Glu Ser Ala  
 485 490 495  
 Asp Leu Asn Gly Lys Leu Arg Gln Val Leu Val Ser His Val Ser His  
 500 505 510  
 Pro Phe Ala Leu Thr Gln Gln Asp Arg Trp Ile Tyr Trp Thr Asp Trp  
 515 520 525  
 Gln Thr Lys Ser Ile Gln Arg Val Asp Lys Tyr Ser Gly Arg Asn Lys  
 530 535 540  
 Glu Thr Val Leu Ala Asn Val Glu Gly Leu Met Asp Ile Ile Val Val  
 545 550 555 560  
 Ser Pro Gln Arg Gln Thr Gly Thr Asn Ala Cys Gly Val Asn Asn Gly  
 565 570 575  
 Gly Cys Thr His Leu Cys Phe Ala Arg Ala Ser Asp Phe Val Cys Ala  
 580 585 590  
 Cys Pro Asp Glu Pro Asp Ser Arg Pro Cys Ser Leu Val Pro Gly Leu  
 595 600 605  
 Val Pro Pro Ala Pro Arg Ala Thr Gly Met Ser Glu Lys Ser Pro Val  
 610 615 620  
 Leu Pro Asn Thr Pro Pro Thr Thr Leu Tyr Ser Ser Thr Thr Arg Thr  
 625 630 635 640  
 Arg Thr Ser Leu Glu Glu Val Glu Gly Arg Cys Ser Glu Arg Asp Ala  
 645 650 655  
 Arg Leu Gly Leu Cys Ala Arg Ser Asn Asp Ala Val Pro Ala Ala Pro  
 660 665 670  
 Gly Glu Gly Leu His Ile Ser Tyr Ala Ile Gly Gly Leu Leu Ser Ile  
 675 680 685  
 Leu Leu Ile Leu Val Val Ile Ala Ala Leu Met Leu Tyr Arg His Lys  
 690 695 700  
 Lys Ser Lys Phe Thr Asp Pro Gly Met Gly Asn Leu Thr Tyr Ser Asn  
 705 710 715 720  
 Pro Ser Tyr Arg Thr Ser Thr Gln Glu Val Lys Ile Glu Ala Ile Pro  
 725 730 735



Nonprovisional IP-017.ST25.txt  
120 125

115

Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu  
 130 135 140  
 Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala  
 145 150 155 160  
 His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Ala Pro Arg Ile Glu  
 165 170 175  
 Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp  
 180 185 190  
 Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu  
 195 200 205  
 Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu Asp  
 210 215 220  
 Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe  
 225 230 235 240  
 Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr  
 245 250 255  
 Arg Ser Ile His Ala Cys Asn Lys Trp Thr Gly Glu Gln Arg Lys Glu  
 260 265 270  
 Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln  
 275 280 285  
 Glu Arg Gln Pro Pro Phe His Thr Pro Cys Glu Glu Asp Asn Gly Gly  
 290 295 300  
 Cys Ser His Leu Cys Leu Leu Ser Pro Arg Glu Pro Phe Tyr Ser Cys  
 305 310 315 320  
 Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Lys Thr Cys Lys  
 325 330 335  
 Thr Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg  
 340 345 350  
 Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val  
 355 360 365  
 Gly Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly  
 370 375 380  
 Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr  
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Nonprovisional IP-017.ST25.txt

385 390 395 400

Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp  
405 410 415

Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr  
420 425 430

Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser  
435 440 445

Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Val  
450 455 460

Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn  
465 470 475 480

Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Arg Asp Arg His Val Leu  
485 490 495

Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln  
500 505 510

Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val  
515 520 525

Ile Asn Ile Asp Gly Thr Lys Arg Lys Thr Leu Leu Glu Asp Lys Leu  
530 535 540

Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr  
545 550 555 560

Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser  
565 570 575

Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala  
580 585 590

Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Gly Asn  
595 600 605

Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro Arg Ala Thr Lys Cys  
610 615 620

Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile  
625 630 635 640

Ile Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Thr Ile His Arg  
645 650 655

Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly

Nonprovisional IP-017.ST25.txt

660

665

670

Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile  
675 680 685

Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn  
690 695 700

Gly Ser Ser Val Glu His Val Ile Glu Phe Gly Leu Asp Tyr Pro Glu  
705 710 715 720

Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr  
725 730 735

Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln  
740 745 750

Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp  
755 760 765

Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg  
770 775 780

Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp  
785 790 795 800

Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg  
805 810 815

Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met  
820 825 830

Leu Gly Gln Glu Arg Met Val Ile Ala Asp Asp Leu Pro Tyr Pro Phe  
835 840 845

Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu  
850 855 860

His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu  
865 870 875 880

Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser  
885 890 895

Ser Arg Gln Asp Gly Leu Asn Asp Cys Val His Ser Asn Gly Gln Cys  
900 905 910

Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala  
915 920 925

Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Ser  
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Nonprovisional IP-017.ST25.txt  
 935 940

930  
 Thr Phe Leu Leu Phe Ser Gln Lys Phe Ala Ile Ser Arg Met Ile Pro  
 945 950 955 960  
 Asp Asp Gln Leu Ser Pro Asp Leu Val Leu Pro Leu His Gly Leu Arg  
 965 970 975  
 Asn Val Lys Ala Ile Asn Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp  
 980 985 990  
 Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr Gln  
 995 1000 1005  
 Pro Ser Met Leu Thr Ser Pro Ser Gln Ser Leu Ser Pro Asp Arg  
 1010 1015 1020  
 Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe  
 1025 1030 1035  
 Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Asp  
 1040 1045 1050  
 Gly Asp Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys Pro  
 1055 1060 1065  
 Arg Ala Ile Ala Val Asn Ala Glu Arg Gly Tyr Met Tyr Phe Thr  
 1070 1075 1080  
 Asn Met Gln Asp His Ala Ala Lys Ile Glu Arg Ala Ser Leu Asp  
 1085 1090 1095  
 Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg Pro  
 1100 1105 1110  
 Val Ala Leu Val Val Asp Asn Ala Leu Gly Lys Leu Phe Trp Val  
 1115 1120 1125  
 Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly Ala  
 1130 1135 1140  
 Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Val Gly  
 1145 1150 1155  
 Leu Thr Val Leu Gly Arg His Leu Tyr Trp Ile Asp Arg Gln Gln  
 1160 1165 1170  
 Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg Thr  
 1175 1180 1185  
 Arg Val Gln Gly Arg Val Thr His Leu Thr Gly Ile His Ala Val  
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Nonprovisional IP-017.ST25.txt  
1195 1200

1190	PROTEIN 1												1200	
Glu 1205	Val	Ser	Leu	Glu 1210	Phe	Ser	Ala	His	Pro 1215	Cys	Ala	Arg		
Asp 1220	Gly	Gly	Cys	Ser	His 1225	Ile	Cys	Ile	Ala	Lys 1230	Gly	Asp	Gly	
Thr 1235	Arg	Cys	Ser	Cys	Pro 1240	Val	His	Leu	Val	Leu 1245	Leu	Gln	Asn	
Leu 1250	Thr	Cys	Gly	Glu	Pro 1255	Pro	Thr	Cys	Ser	Pro 1260	Asp	Gln	Phe	
Ala 1265	Cys	Thr	Thr	Gly	Glu	Ile 1270	Asp	Cys	Ile	Pro	Gly 1275	Ala	Trp	Arg
Cys 1280	Asp	Gly	Phe	Pro	Glu	Cys 1285	Ala	Asp	Gln	Ser	Asp 1290	Glu	Glu	Gly
Cys 1295	Pro	Val	Cys	Ser	Ala	Ser 1300	Gln	Phe	Pro	Cys	Ala 1305	Arg	Gly	Gln
Cys 1310	Val	Asp	Leu	Arg	Leu	Arg 1315	Cys	Asp	Gly	Glu	Ala 1320	Asp	Cys	Gln
Asp 1325	Arg	Ser	Asp	Glu	Ala	Asn 1330	Cys	Asp	Ala	Val	Cys 1335	Leu	Pro	Asn
Gln 1340	Phe	Arg	Cys	Thr	Ser	Gly 1345	Gln	Cys	Val	Leu	Ile 1350	Lys	Gln	Gln
Cys 1355	Asp	Ser	Phe	Pro	Asp	Cys 1360	Ala	Asp	Gly	Ser	Asp 1365	Glu	Leu	Met
Cys 1370	Glu	Ile	Asn	Lys	Pro	Pro 1375	Ser	Asp	Asp	Ile	Pro 1380	Ala	His	Ser
Ser 1385	Ala	Ile	Gly	Pro	Val	Ile 1390	Gly	Ile	Ile	Leu	Ser 1395	Leu	Phe	Val
Met 1400	Gly	Gly	Val	Tyr	Phe	Val 1405	Cys	Gln	Arg	Val	Met 1410	Cys	Gln	Arg
Tyr 1415	Thr	Gly	Ala	Ser	Gly	Pro 1420	Phe	Pro	His	Glu	Tyr 1425	Val	Gly	Gly
Ala 1430	Pro	His	Val	Pro	Leu	Asn 1435	Phe	Ile	Ala	Pro	Gly 1440	Gly	Ser	Gln
His 1445	Gly	Pro	Phe	Pro	Gly	Ile	Pro	Cys	Ser	Lys	Ser 1445	Val	Met	Ser

Nonprovisional IP-017.ST25.txt

1445  
 1450  
 1455  
 Ser Met Ser Leu Val Gly Gly Arg Gly Ser Val Pro Leu Tyr Asp  
 1460 1465 1470  
 Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser Thr  
 1475 1480 1485  
 Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro  
 1490 1495 1500  
 Ala Thr Asp Pro Ser Leu Tyr Asn Val Asp Val Phe Tyr Ser Ser  
 1505 1510 1515  
 Gly Ile Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Val Ile Arg  
 1520 1525 1530  
 Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp  
 1535 1540 1545  
 Ser Asp Tyr Ser Ile Ser Arg Trp Lys Ser Ser Lys Tyr Tyr Leu  
 1550 1555 1560  
 Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro  
 1565 1570 1575  
 His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro  
 1580 1585 1590  
 Gly Thr Glu Arg Ser Tyr Cys His Leu Phe Pro Pro Pro Pro Ser  
 1595 1600 1605  
 Pro Cys Thr Asp Ser Ser  
 1610

<210> 81  
 <211> 1611  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 81

Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu  
 1 5 10 15  
 Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser  
 20 25 30  
 Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala  
 35 40 45  
 Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp  
 50 55 60

## Nonprovisional IP-017.ST25.txt

Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr  
 65 70 75 80  
 Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly  
 85 90 95  
 Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly  
 100 105 110  
 Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu  
 115 120 125  
 Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val  
 130 135 140  
 Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro  
 145 150 155 160  
 Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile  
 165 170 175  
 Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser  
 180 185 190  
 Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys  
 195 200 205  
 Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu  
 210 215 220  
 Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro  
 225 230 235 240  
 Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln  
 245 250 255  
 Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys  
 260 265 270  
 Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser  
 275 280 285  
 Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly  
 290 295 300  
 Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr  
 305 310 315 320  
 Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys  
 325 330 335

## Nonprovisional IP-017.ST25.txt

Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu  
 340 345 350  
 Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln  
 355 360 365  
 Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu  
 370 375 380  
 Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala  
 385 390 395 400  
 Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn  
 405 410 415  
 Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp  
 420 425 430  
 Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr  
 435 440 445  
 Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile  
 450 455 460  
 Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu  
 465 470 475 480  
 Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val  
 485 490 495  
 Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu  
 500 505 510  
 Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu  
 515 520 525  
 Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys  
 530 535 540  
 Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp  
 545 550 555 560  
 Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala  
 565 570 575  
 Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys  
 580 585 590  
 Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg  
 595 600 605

## Nonprovisional IP-017.ST25.txt

Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg  
 610 615 620  
 Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys  
 625 630 635 640  
 Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His  
 645 650 655  
 Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr  
 660 665 670  
 Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His  
 675 680 685  
 Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met  
 690 695 700  
 Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro  
 705 710 715 720  
 Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp  
 725 730 735  
 Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg  
 740 745 750  
 Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu  
 755 760 765  
 Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro  
 770 775 780  
 Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val  
 785 790 795 800  
 Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln  
 805 810 815  
 Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn  
 820 825 830  
 Met Leu Gly Gln Glu Arg Val Val Ile Ala Asp Asp Leu Pro His Pro  
 835 840 845  
 Phe Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn  
 850 855 860  
 Leu His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr  
 865 870 875 880

## Nonprovisional IP-017.ST25.txt

Leu Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His  
 885 890 895  
 Ser Ser Arg Gln Asp Gly Leu Asn Asp Cys Met His Asn Asn Gly Gln  
 900 905 910  
 Cys Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys  
 915 920 925  
 Ala Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro  
 930 935 940  
 Thr Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile Ser Arg Met Ile  
 945 950 955 960  
 Pro Asp Asp Gln His Ser Pro Asp Leu Ile Leu Pro Leu His Gly Leu  
 965 970 975  
 Arg Asn Val Lys Ala Ile Asp Tyr Asp Pro Leu Asp Lys Phe Ile Tyr  
 980 985 990  
 Trp Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr  
 995 1000 1005  
 Gln Pro Phe Val Leu Thr Ser Leu Ser Gln Gly Gln Asn Pro Asp  
 1010 1015 1020  
 Arg Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu  
 1025 1030 1035  
 Phe Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu  
 1040 1045 1050  
 Ser Gly Glu Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys  
 1055 1060 1065  
 Pro Arg Ala Ile Val Val Asn Ala Glu Arg Gly Tyr Leu Tyr Phe  
 1070 1075 1080  
 Thr Asn Met Gln Asp Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu  
 1085 1090 1095  
 Asp Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg  
 1100 1105 1110  
 Pro Val Ala Leu Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp  
 1115 1120 1125  
 Val Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly  
 1130 1135 1140

## Nonprovisional IP-017.ST25.txt

Ala Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Leu  
 1145 1150 1155  
 Gly Leu Thr Ile Leu Gly Lys His Leu Tyr Trp Ile Asp Arg Gln  
 1160 1165 1170  
 Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg  
 1175 1180 1185  
 Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly Ile His Ala  
 1190 1195 1200  
 Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala  
 1205 1210 1215  
 Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp  
 1220 1225 1230  
 Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln  
 1235 1240 1245  
 Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln  
 1250 1255 1260  
 Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp  
 1265 1270 1275  
 Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu  
 1280 1285 1290  
 Gly Cys Pro Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly  
 1295 1300 1305  
 Gln Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys  
 1310 1315 1320  
 Gln Asp Arg Ser Asp Glu Ala Asp Cys Asp Ala Ile Cys Leu Pro  
 1325 1330 1335  
 Asn Gln Phe Arg Cys Ala Ser Gly Gln Cys Val Leu Ile Lys Gln  
 1340 1345 1350  
 Gln Cys Asp Ser Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu Leu  
 1355 1360 1365  
 Met Cys Glu Ile Thr Lys Pro Pro Ser Asp Asp Ser Pro Ala His  
 1370 1375 1380  
 Ser Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe  
 1385 1390 1395

## Nonprovisional IP-017.ST25.txt

Val Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Val Cys Gln  
 1400 1405 1410  
 Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His Glu Tyr Val Ser  
 1415 1420 1425  
 Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser  
 1430 1435 1440  
 Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met  
 1445 1450 1455  
 Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr  
 1460 1465 1470  
 Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser  
 1475 1480 1485  
 Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser  
 1490 1495 1500  
 Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser  
 1505 1510 1515  
 Ser Asn Ile Pro Ala Thr Arg Pro Tyr Ile Ile Arg Gly Met Ala  
 1520 1525 1530  
 Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp Ser Asp Tyr  
 1535 1540 1545  
 Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr Leu Asp Leu Asn  
 1550 1555 1560  
 Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro His Ser Gln  
 1565 1570 1575  
 Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro Ala Thr Glu  
 1580 1585 1590  
 Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro Ser Pro Cys Thr  
 1595 1600 1605  
 Asp Ser Ser  
 1610

<210> 82  
 <211> 1615  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 82



## Nonprovisional IP-017.ST25.txt

Met Glu Ala Ala Pro Pro Gly Pro Pro Trp Pro Leu Leu Leu Leu Leu  
 1 5 10 15  
 Leu Leu Leu Leu Ala Leu Cys Gly Cys Pro Ala Pro Ala Ala Ala Ser  
 20 25 30  
 Pro Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala  
 35 40 45  
 Gly Gly Val Lys Leu Glu Ser Thr Ile Val Val Ser Gly Leu Glu Asp  
 50 55 60  
 Ala Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr  
 65 70 75 80  
 Asp Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly  
 85 90 95  
 Ala Ala Val Gln Asn Val Val Ile Ser Gly Leu Val Ser Pro Asp Gly  
 100 105 110  
 Leu Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu  
 115 120 125  
 Thr Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val  
 130 135 140  
 Leu Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro  
 145 150 155 160  
 Ala His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Thr Pro Arg Ile  
 165 170 175  
 Glu Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser  
 180 185 190  
 Asp Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys  
 195 200 205  
 Leu Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu  
 210 215 220  
 Asp Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro  
 225 230 235 240  
 Phe Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln  
 245 250 255  
 Thr Arg Ser Ile His Ala Cys Asn Lys Arg Thr Gly Gly Lys Arg Lys  
 260 265 270

## Nonprovisional IP-017.ST25.txt

Glu Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser  
 275 280 285  
 Gln Glu Arg Gln Pro Phe Phe His Thr Arg Cys Glu Glu Asp Asn Gly  
 290 295 300  
 Gly Cys Ser His Leu Cys Leu Leu Ser Pro Ser Glu Pro Phe Tyr Thr  
 305 310 315 320  
 Cys Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Arg Thr Cys  
 325 330 335  
 Lys Ala Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu  
 340 345 350  
 Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln  
 355 360 365  
 Val Asp Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu  
 370 375 380  
 Gly Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala  
 385 390 395 400  
 Tyr Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn  
 405 410 415  
 Asp Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp  
 420 425 430  
 Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr  
 435 440 445  
 Ser Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile  
 450 455 460  
 Ala Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu  
 465 470 475 480  
 Asn Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Gln Glu Arg Arg Val  
 485 490 495  
 Leu Val Asn Ala Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu  
 500 505 510  
 Gln Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu  
 515 520 525  
 Val Ile Asn Val Asp Gly Thr Lys Arg Arg Thr Leu Leu Glu Asp Lys  
 530 535 540

## Nonprovisional IP-017.ST25.txt

Leu Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp  
 545 550 555 560  
 Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala  
 565 570 575  
 Ser Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys  
 580 585 590  
 Ala Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Arg  
 595 600 605  
 Asn Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro His Ala Thr Arg  
 610 615 620  
 Cys Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys  
 625 630 635 640  
 Ile Val Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Ala Ile His  
 645 650 655  
 Arg Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr  
 660 665 670  
 Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His  
 675 680 685  
 Ile Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met  
 690 695 700  
 Asn Gly Ser Ser Val Glu His Val Val Glu Phe Gly Leu Asp Tyr Pro  
 705 710 715 720  
 Glu Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp  
 725 730 735  
 Thr Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg  
 740 745 750  
 Gln Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu  
 755 760 765  
 Asp Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro  
 770 775 780  
 Arg Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val  
 785 790 795 800  
 Asp Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln  
 805 810 815

## Nonprovisional IP-017.ST25.txt

Arg	Leu	Tyr	Trp	Thr	Asp	Leu	Asp	Thr	Asn	Met	Ile	Glu	Ser	Ser	Asn
			820					825					830		
Met	Leu	Gly	Gln	Glu	Arg	Val	Val	Ile	Ala	Asp	Asp	Leu	Pro	His	Pro
		835					840					845			
Phe	Gly	Leu	Thr	Gln	Tyr	Ser	Asp	Tyr	Ile	Tyr	Trp	Thr	Asp	Trp	Asn
	850					855					860				
Leu	His	Ser	Ile	Glu	Arg	Ala	Asp	Lys	Thr	Ser	Gly	Arg	Asn	Arg	Thr
865					870					875					880
Leu	Ile	Gln	Gly	His	Leu	Asp	Phe	Val	Met	Asp	Ile	Leu	Val	Phe	His
				885					890					895	
Ser	Ser	Arg	Gln	Asp	Gly	Leu	Asn	Asp	Cys	Met	His	Asn	Asn	Gly	Gln
			900					905					910		
Cys	Gly	Gln	Leu	Cys	Leu	Ala	Ile	Pro	Gly	Gly	His	Arg	Cys	Gly	Cys
		915					920					925			
Ala	Ser	His	Tyr	Thr	Leu	Asp	Pro	Ser	Ser	Arg	Asn	Cys	Ser	Pro	Pro
	930					935					940				
Thr	Thr	Phe	Leu	Leu	Phe	Ser	Gln	Lys	Ser	Ala	Ile	Ser	Arg	Met	Ile
945					950					955					960
Pro	Asp	Asp	Gln	His	Ser	Pro	Asp	Leu	Ile	Leu	Pro	Leu	His	Gly	Leu
				965					970					975	
Arg	Asn	Val	Lys	Ala	Ile	Asp	Tyr	Asp	Pro	Leu	Asp	Lys	Phe	Ile	Tyr
			980					985					990		
Trp	Val	Asp	Gly	Arg	Gln	Asn	Ile	Lys	Arg	Ala	Lys	Asp	Asp	Gly	Thr
		995					1000					1005			
Gln	Pro	Phe	Val	Leu	Thr	Ser	Leu	Ser	Gln	Gly	Gln	Asn	Pro	Asp	
	1010					1015					1020				
Arg	Gln	Pro	His	Asp	Leu	Ser	Ile	Asp	Ile	Tyr	Ser	Arg	Thr	Leu	
	1025					1030					1035				
Phe	Trp	Thr	Cys	Glu	Ala	Thr	Asn	Thr	Ile	Asn	Val	His	Arg	Leu	
	1040					1045					1050				
Ser	Gly	Glu	Ala	Met	Gly	Val	Val	Leu	Arg	Gly	Asp	Arg	Asp	Lys	
	1055					1060					1065				
Pro	Arg	Ala	Ile	Val	Val	Asn	Ala	Glu	Arg	Gly	Tyr	Leu	Tyr	Phe	
	1070					1075					1080				

## Nonprovisional IP-017.ST25.txt

Thr Asn Met Gln Asp Arg Ala Ala Lys Ile Glu Arg Ala Ala Leu  
 1085 1090 1095  
 Asp Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg  
 1100 1105 1110  
 Pro Val Ala Leu Val Val Asp Asn Thr Leu Gly Lys Leu Phe Trp  
 1115 1120 1125  
 Val Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly  
 1130 1135 1140  
 Ala Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Leu  
 1145 1150 1155  
 Gly Leu Thr Ile Leu Gly Lys His Leu Tyr Trp Ile Asp Arg Gln  
 1160 1165 1170  
 Gln Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg  
 1175 1180 1185  
 Thr Arg Ile Gln Gly Arg Val Ala His Leu Thr Gly Ile His Ala  
 1190 1195 1200  
 Val Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala  
 1205 1210 1215  
 Arg Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp  
 1220 1225 1230  
 Gly Thr Pro Arg Cys Ser Cys Pro Val His Leu Val Leu Leu Gln  
 1235 1240 1245  
 Asn Leu Leu Thr Cys Gly Glu Pro Pro Thr Cys Ser Pro Asp Gln  
 1250 1255 1260  
 Phe Ala Cys Ala Thr Gly Glu Ile Asp Cys Ile Pro Gly Ala Trp  
 1265 1270 1275  
 Arg Cys Asp Gly Phe Pro Glu Cys Asp Asp Gln Ser Asp Glu Glu  
 1280 1285 1290  
 Gly Cys Pro Val Cys Ser Ala Ala Gln Phe Pro Cys Ala Arg Gly  
 1295 1300 1305  
 Gln Cys Val Asp Leu Arg Leu Arg Cys Asp Gly Glu Ala Asp Cys  
 1310 1315 1320  
 Gln Asp Arg Ser Asp Glu Ala Asp Cys Asp Ala Ile Cys Leu Pro  
 1325 1330 1335

## Nonprovisional IP-017.ST25.txt

Asn Gln Phe Arg Cys Ala Ser Gly Gln Cys Val Leu Ile Lys Gln  
 1340 1345 1350  
 Gln Cys Asp Ser Phe Pro Asp Cys Ile Asp Gly Ser Asp Glu Leu  
 1355 1360 1365  
 Met Cys Glu Ile Thr Lys Pro Pro Ser Asp Asp Ser Pro Ala His  
 1370 1375 1380  
 Ser Ser Ala Ile Gly Pro Val Ile Gly Ile Ile Leu Ser Leu Phe  
 1385 1390 1395  
 Val Met Gly Gly Val Tyr Phe Val Cys Gln Arg Val Val Cys Gln  
 1400 1405 1410  
 Arg Tyr Ala Gly Ala Asn Gly Pro Phe Pro His Glu Tyr Val Ser  
 1415 1420 1425  
 Gly Thr Pro His Val Pro Leu Asn Phe Ile Ala Pro Gly Gly Ser  
 1430 1435 1440  
 Gln His Gly Pro Phe Thr Gly Ile Ala Cys Gly Lys Ser Met Met  
 1445 1450 1455  
 Ser Ser Val Ser Leu Met Gly Gly Arg Gly Gly Val Pro Leu Tyr  
 1460 1465 1470  
 Asp Arg Asn His Val Thr Gly Ala Ser Ser Ser Ser Ser Ser Ser  
 1475 1480 1485  
 Thr Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser  
 1490 1495 1500  
 Pro Ala Thr Asp Pro Ser Leu Tyr Asn Met Asp Met Phe Tyr Ser  
 1505 1510 1515  
 Ser Asn Ile Pro Ala Thr Val Arg Pro Tyr Arg Pro Tyr Ile Ile  
 1520 1525 1530  
 Arg Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys  
 1535 1540 1545  
 Asp Ser Asp Tyr Ser Ala Ser Arg Trp Lys Ala Ser Lys Tyr Tyr  
 1550 1555 1560  
 Leu Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr  
 1565 1570 1575  
 Pro His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser  
 1580 1585 1590

## Nonprovisional IP-017.ST25.txt

Pro Ala Thr Glu Arg Ser Tyr Phe His Leu Phe Pro Pro Pro Pro  
 1595 1600 1605

Ser Pro Cys Thr Asp Ser Ser  
 1610 1615

<210> 83  
 <211> 1613  
 <212> PRT  
 <213> MOUSE

<400> 83

Met Gly Ala Val Leu Arg Ser Leu Leu Ala Cys Ser Phe Cys Val Leu  
 1 5 10 15

Leu Arg Ala Ala Pro Leu Leu Leu Tyr Ala Asn Arg Arg Asp Leu Arg  
 20 25 30

Leu Val Asp Ala Thr Asn Gly Lys Glu Asn Ala Thr Ile Val Val Gly  
 35 40 45

Gly Leu Glu Asp Ala Ala Ala Val Asp Phe Val Phe Gly His Gly Leu  
 50 55 60

Ile Tyr Trp Ser Asp Val Ser Glu Glu Ala Ile Lys Arg Thr Glu Phe  
 65 70 75 80

Asn Lys Ser Glu Ser Val Gln Asn Val Val Val Ser Gly Leu Leu Ser  
 85 90 95

Pro Asp Gly Leu Ala Cys Asp Trp Leu Gly Glu Lys Leu Tyr Trp Thr  
 100 105 110

Asp Ser Glu Thr Asn Arg Ile Glu Val Ser Asn Leu Asp Gly Ser Leu  
 115 120 125

Arg Lys Val Leu Phe Trp Gln Glu Leu Asp Gln Pro Arg Ala Ile Ala  
 130 135 140

Leu Asp Pro Ser Ser Gly Phe Met Tyr Trp Thr Asp Trp Gly Glu Val  
 145 150 155 160

Pro Lys Ile Glu Arg Ala Gly Met Asp Gly Ser Ser Arg Phe Val Ile  
 165 170 175

Ile Asn Thr Glu Ile Tyr Trp Pro Asn Gly Leu Thr Leu Asp Tyr Gln  
 180 185 190

Glu Arg Lys Leu Tyr Trp Ala Asp Ala Lys Leu Asn Phe Ile His Lys  
 195 200 205

## Nonprovisional IP-017.ST25.txt

Ser Asn Leu Asp Gly Thr Asn Arg Gln Ala Val Val Lys Gly Ser Leu  
 210 215 220  
 Pro His Pro Phe Ala Leu Thr Leu Phe Glu Asp Thr Leu Tyr Trp Thr  
 225 230 235 240  
 Asp Trp Asn Thr His Ser Ile Leu Ala Cys Asn Lys Tyr Thr Gly Glu  
 245 250 255  
 Gly Leu Arg Glu Ile His Ser Asn Ile Phe Ser Pro Met Asp Ile His  
 260 265 270  
 Ala Phe Ser Gln Gln Arg Gln Pro Asn Ala Thr Asn Pro Cys Gly Ile  
 275 280 285  
 Asp Asn Gly Gly Cys Ser His Leu Cys Leu Met Ser Pro Val Lys Pro  
 290 295 300  
 Phe Tyr Gln Cys Ala Cys Pro Thr Gly Val Lys Leu Met Glu Asn Gly  
 305 310 315 320  
 Lys Thr Cys Lys Asp Gly Ala Thr Glu Leu Leu Leu Leu Ala Arg Arg  
 325 330 335  
 Thr Asp Leu Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile  
 340 345 350  
 Val Leu Gln Leu Glu Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp  
 355 360 365  
 Pro Val Glu Gly Tyr Ile Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile  
 370 375 380  
 Arg Arg Ser Phe Ile Asp Gly Ser Gly Ser Gln Phe Val Val Thr Ala  
 385 390 395 400  
 Gln Ile Ala His Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn  
 405 410 415  
 Leu Tyr Trp Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu  
 420 425 430  
 Asn Gly Thr Met Arg Lys Ile Leu Ile Ser Glu Asp Leu Glu Glu Pro  
 435 440 445  
 Arg Ala Ile Val Leu Asp Pro Met Val Gly Tyr Met Tyr Trp Thr Asp  
 450 455 460  
 Trp Gly Glu Ile Pro Lys Ile Glu Arg Ala Ala Leu Asp Gly Ser Asp  
 465 470 475 480



## Nonprovisional IP-017.ST25.txt

Arg Val Val Leu Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala  
 485 490 495  
 Leu Asp Tyr Asp Glu Gly Thr Ile Tyr Trp Gly Asp Ala Lys Thr Asp  
 500 505 510  
 Lys Ile Glu Val Met Asn Thr Asp Gly Thr Gly Arg Arg Val Leu Val  
 515 520 525  
 Glu Asp Lys Ile Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Tyr  
 530 535 540  
 Val Tyr Trp Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys  
 545 550 555 560  
 Arg Ser Ala Glu Arg Glu Val Ile Ile Asp Gln Leu Pro Asp Leu Met  
 565 570 575  
 Gly Leu Lys Ala Thr Ser Val His Arg Val Ile Gly Ser Asn Pro Cys  
 580 585 590  
 Ala Glu Asp Asn Gly Gly Cys Ser His Leu Cys Leu Tyr Arg Pro Gln  
 595 600 605  
 Gly Leu Arg Cys Ala Cys Pro Ile Gly Phe Glu Leu Ile Gly Asp Met  
 610 615 620  
 Lys Thr Cys Ile Val Pro Glu Ala Phe Leu Leu Phe Ser Arg Arg Ala  
 625 630 635 640  
 Asp Ile Arg Arg Ile Ser Leu Glu Thr Asn Asn Asn Asn Val Ala Ile  
 645 650 655  
 Pro Leu Thr Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Thr  
 660 665 670  
 Asp Asn Arg Ile Tyr Trp Thr Asp Ile Ser Leu Lys Thr Ile Ser Arg  
 675 680 685  
 Ala Phe Met Asn Gly Ser Ala Leu Glu His Val Val Glu Phe Gly Leu  
 690 695 700  
 Asp Tyr Pro Glu Gly Met Ala Val Asp Trp Leu Gly Lys Asn Leu Tyr  
 705 710 715 720  
 Trp Ala Asp Thr Gly Thr Asn Arg Ile Glu Val Ser Lys Leu Asp Gly  
 725 730 735  
 Gln His Arg Gln Val Leu Val Trp Lys Asp Leu Asp Ser Pro Arg Ala  
 740 745 750

## Nonprovisional IP-017.ST25.txt

Leu Ala Leu Asp Pro Ala Glu Gly Phe Met Tyr Trp Thr Glu Trp Gly  
 755 760 765  
 Gly Lys Pro Lys Ile Asp Arg Ala Ala Met Asp Gly Ser Glu Arg Thr  
 770 775 780  
 Thr Leu Val Pro Asn Val Gly Arg Ala Asn Gly Leu Thr Ile Asp Tyr  
 785 790 795 800  
 Ala Lys Arg Arg Leu Tyr Trp Thr Asp Leu Asp Thr Asn Leu Ile Glu  
 805 810 815  
 Ser Ser Asp Met Leu Gly Leu Asn Arg Glu Val Ile Ala Asp Asp Leu  
 820 825 830  
 Pro His Pro Phe Gly Leu Thr Gln Tyr Gln Asp Tyr Ile Tyr Trp Thr  
 835 840 845  
 Asp Trp Ser Arg Arg Ser Ile Glu Arg Ala Asn Lys Thr Ser Gly Gln  
 850 855 860  
 Asn Arg Thr Ile Ile Gln Gly His Leu Asp Tyr Val Met Asp Ile Leu  
 865 870 875 880  
 Val Phe His Ser Ser Arg Gln Ala Gly Trp Asn Glu Cys Ala Ser Ser  
 885 890 895  
 Asn Gly His Cys Ser His Leu Cys Leu Ala Val Pro Val Gly Gly Phe  
 900 905 910  
 Val Cys Gly Cys Pro Ala His Tyr Ser Leu Asn Ala Asp Asn Arg Thr  
 915 920 925  
 Cys Ser Ala Pro Ser Thr Phe Leu Leu Phe Ser Gln Lys Ser Ala Ile  
 930 935 940  
 Asn Arg Met Val Ile Asp Glu Gln Gln Ser Pro Asp Ile Ile Leu Pro  
 945 950 955 960  
 Ile His Ser Leu Arg Asn Val Arg Ala Ile Asp Tyr Asp Pro Leu Asp  
 965 970 975  
 Lys Gln Leu Tyr Trp Ile Asp Ser Arg Gln Asn Ser Ile Arg Lys Ala  
 980 985 990  
 His Glu Asp Gly Gly Gln Gly Phe Asn Val Val Ala Asn Ser Val Ala  
 995 1000 1005  
 Asn Gln Asn Leu Glu Ile Gln Pro Tyr Asp Leu Ser Ile Asp Ile  
 1010 1015 1020

Nonprovisional IP-017.ST25.txt

Tyr	Ser	Arg	Tyr	Ile	Tyr	Trp	Thr	Cys	Glu	Ala	Thr	Asn	Val	Ile
	1025					1030					1035			
Asp	Val	Thr	Arg	Leu	Asp	Gly	Arg	Ser	Val	Gly	Val	Val	Leu	Lys
	1040					1045					1050			
Gly	Glu	Gln	Asp	Arg	Pro	Arg	Ala	Ile	Val	Val	Asn	Pro	Glu	Lys
	1055					1060					1065			
Gly	Tyr	Met	Tyr	Phe	Thr	Asn	Leu	Gln	Glu	Arg	Ser	Pro	Lys	Ile
	1070					1075					1080			
Glu	Arg	Ala	Ala	Leu	Asp	Gly	Thr	Glu	Arg	Glu	Val	Leu	Phe	Phe
	1085					1090					1095			
Ser	Gly	Leu	Ser	Lys	Pro	Ile	Ala	Leu	Ala	Leu	Asp	Ser	Lys	Leu
	1100					1105					1110			
Gly	Lys	Leu	Phe	Trp	Ala	Asp	Ser	Asp	Leu	Arg	Arg	Ile	Glu	Ser
	1115					1120					1125			
Ser	Asp	Leu	Ser	Gly	Ala	Asn	Arg	Ile	Val	Leu	Glu	Asp	Ser	Asn
	1130					1135					1140			
Ile	Leu	Gln	Pro	Val	Gly	Leu	Thr	Val	Phe	Glu	Asn	Trp	Leu	Tyr
	1145					1150					1155			
Trp	Ile	Asp	Lys	Gln	Gln	Gln	Met	Ile	Glu	Lys	Ile	Asp	Met	Thr
	1160					1165					1170			
Gly	Arg	Glu	Gly	Arg	Thr	Lys	Val	Gln	Ala	Arg	Ile	Ala	Gln	Leu
	1175					1180					1185			
Ser	Asp	Ile	His	Ala	Val	Lys	Glu	Leu	Asn	Leu	Gln	Glu	Tyr	Arg
	1190					1195					1200			
Gln	His	Pro	Cys	Ala	Gln	Asp	Asn	Gly	Gly	Cys	Ser	His	Ile	Cys
	1205					1210					1215			
Leu	Val	Lys	Gly	Asp	Gly	Thr	Thr	Arg	Cys	Ser	Cys	Pro	Met	His
	1220					1225					1230			
Leu	Val	Leu	Leu	Gln	Asp	Glu	Leu	Ser	Cys	Gly	Glu	Pro	Pro	Thr
	1235					1240					1245			
Cys	Ser	Pro	Gln	Gln	Phe	Thr	Cys	Phe	Thr	Gly	Asp	Ile	Asp	Cys
	1250					1255					1260			
Ile	Pro	Val	Ala	Trp	Arg	Cys	Asp	Gly	Phe	Thr	Glu	Cys	Glu	Asp
	1265					1270					1275			

Nonprovisional IP-017.ST25.txt

His	Ser	Asp	Glu	Leu	Asn	Cys	Pro	Val	Cys	Ser	Glu	Ser	Gln	Phe
	1280					1285					1290			
Gln	Cys	Ala	Ser	Gly	Gln	Cys	Ile	Asp	Gly	Ala	Leu	Arg	Cys	Asn
	1295					1300					1305			
Gly	Asp	Ala	Asn	Cys	Gln	Asp	Lys	Ser	Asp	Glu	Lys	Asn	Cys	Glu
	1310					1315					1320			
Val	Leu	Cys	Leu	Ile	Asp	Gln	Phe	Arg	Cys	Ala	Asn	Gly	Gln	Cys
	1325					1330					1335			
Val	Gly	Lys	His	Lys	Lys	Cys	Asp	His	Ser	Val	Asp	Cys	Ser	Asp
	1340					1345					1350			
Arg	Ser	Asp	Glu	Leu	Asp	Cys	Tyr	Pro	Thr	Glu	Glu	Pro	Ala	Pro
	1355					1360					1365			
Gln	Ala	Thr	Asn	Thr	Val	Gly	Ser	Val	Ile	Gly	Val	Ile	Val	Thr
	1370					1375					1380			
Ile	Phe	Val	Ser	Gly	Thr	Ile	Tyr	Phe	Ile	Cys	Gln	Arg	Met	Leu
	1385					1390					1395			
Cys	Pro	Arg	Met	Lys	Gly	Asp	Gly	Glu	Thr	Met	Thr	Asn	Asp	Tyr
	1400					1405					1410			
Val	Val	His	Ser	Pro	Ala	Ser	Val	Pro	Leu	Gly	Tyr	Val	Pro	His
	1415					1420					1425			
Pro	Ser	Ser	Leu	Ser	Gly	Ser	Leu	Pro	Gly	Met	Ser	Arg	Gly	Lys
	1430					1435					1440			
Ser	Met	Ile	Ser	Ser	Leu	Ser	Ile	Met	Gly	Gly	Ser	Ser	Gly	Pro
	1445					1450					1455			
Pro	Tyr	Asp	Arg	Ala	His	Val	Thr	Gly	Ala	Ser	Ser	Ser	Ser	Ser
	1460					1465					1470			
Ser	Ser	Thr	Lys	Gly	Thr	Tyr	Phe	Pro	Ala	Ile	Leu	Asn	Pro	Pro
	1475					1480					1485			
Pro	Ser	Pro	Ala	Thr	Glu	Arg	Ser	His	Tyr	Thr	Met	Glu	Phe	Gly
	1490					1495					1500			
Tyr	Ser	Ser	Asn	Ser	Pro	Ser	Thr	His	Arg	Ser	Tyr	Ser	Tyr	Arg
	1505					1510					1515			
Pro	Tyr	Ser	Tyr	Arg	His	Phe	Ala	Pro	Pro	Thr	Thr	Pro	Cys	Ser
	1520					1525					1530			

## Nonprovisional IP-017.ST25.txt

Thr Asp Val Cys Asp Ser Asp Tyr Ala Pro Ser Arg Arg Met Thr  
 1535 1540 1545

Ser Val Ala Thr Ala Lys Gly Tyr Thr Ser Asp Val Asn Tyr Asp  
 1550 1555 1560

Ser Glu Pro Val Pro Pro Pro Thr Pro Arg Ser Gln Tyr Leu  
 1565 1570 1575

Ser Ala Glu Glu Asn Tyr Glu Ser Cys Pro Pro Ser Pro Tyr Thr  
 1580 1585 1590

Glu Arg Ser Tyr Ser His His Leu Tyr Pro Pro Pro Ser Pro  
 1595 1600 1605

Cys Thr Asp Ser Ser  
 1610

<210> 84  
 <211> 1613  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 84

Met Gly Ala Val Leu Arg Ser Leu Leu Ala Cys Ser Phe Cys Val Leu  
 1 5 10 15

Leu Arg Ala Ala Pro Leu Leu Leu Tyr Ala Asn Arg Arg Asp Leu Arg  
 20 25 30

Leu Val Asp Ala Thr Asn Gly Lys Glu Asn Ala Thr Ile Val Val Gly  
 35 40 45

Gly Leu Glu Asp Ala Ala Ala Val Asp Phe Val Phe Ser His Gly Leu  
 50 55 60

Ile Tyr Trp Ser Asp Val Ser Glu Glu Ala Ile Lys Arg Thr Glu Phe  
 65 70 75 80

Asn Lys Thr Glu Ser Val Gln Asn Val Val Val Ser Gly Leu Leu Ser  
 85 90 95

Pro Asp Gly Leu Ala Cys Asp Trp Leu Gly Glu Lys Leu Tyr Trp Thr  
 100 105 110

Asp Ser Glu Thr Asn Arg Ile Glu Val Ser Asn Leu Asp Gly Ser Leu  
 115 120 125

Arg Lys Val Leu Phe Trp Gln Glu Leu Asp Gln Pro Arg Ala Ile Ala  
 130 135 140

Leu Asp Pro Ser Ser Gly Phe Met Tyr Trp Thr Asp Trp Gly Glu Val  
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Nonprovisional IP-017.ST25.txt

145 150 155 160

Pro Lys Ile Glu Arg Ala Gly Met Asp Gly Ser Ser Arg Phe Ile Ile  
165 170 175

Ile Asn Ser Glu Ile Tyr Trp Pro Asn Gly Leu Thr Leu Asp Tyr Glu  
180 185 190

Glu Gln Lys Leu Tyr Trp Ala Asp Ala Lys Leu Asn Phe Ile His Lys  
195 200 205

Ser Asn Leu Asp Gly Thr Asn Arg Gln Ala Val Val Lys Gly Ser Leu  
210 215 220

Pro His Pro Phe Ala Leu Thr Leu Phe Glu Asp Ile Leu Tyr Trp Thr  
225 230 235 240

Asp Trp Ser Thr His Ser Ile Leu Ala Cys Asn Lys Tyr Thr Gly Glu  
245 250 255

Gly Leu Arg Glu Ile His Ser Asp Ile Phe Ser Pro Met Asp Ile His  
260 265 270

Ala Phe Ser Gln Gln Arg Gln Pro Asn Ala Thr Asn Pro Cys Gly Ile  
275 280 285

Asp Asn Gly Gly Cys Ser His Leu Cys Leu Met Ser Pro Val Lys Pro  
290 295 300

Phe Tyr Gln Cys Ala Cys Pro Thr Gly Val Lys Leu Leu Glu Asn Gly  
305 310 315 320

Lys Thr Cys Lys Asp Gly Ala Thr Glu Leu Leu Leu Ala Arg Arg  
325 330 335

Thr Asp Leu Arg Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile  
340 345 350

Val Leu Gln Leu Glu Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp  
355 360 365

Pro Val Glu Gly Tyr Ile Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile  
370 375 380

Arg Arg Ser Phe Ile Asp Gly Ser Gly Ser Gln Phe Val Val Thr Ala  
385 390 395 400

Gln Ile Ala His Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn  
405 410 415

Leu Tyr Trp Thr Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu

Nonprovisional IP-017.ST25.txt

420

425

430

Asn Gly Thr Met Arg Lys Ile Leu Ile Ser Glu Asp Leu Glu Glu Pro  
 435 440 445

Arg Ala Ile Val Leu Asp Pro Met Val Gly Tyr Met Tyr Trp Thr Asp  
 450 455 460

Trp Gly Glu Ile Pro Lys Ile Glu Arg Ala Ala Leu Asp Gly Ser Asp  
 465 470 475 480

Arg Val Val Leu Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala  
 485 490 495

Leu Asp Tyr Asp Glu Gly Lys Ile Tyr Trp Gly Asp Ala Lys Thr Asp  
 500 505 510

Lys Ile Glu Val Met Asn Thr Asp Gly Thr Gly Arg Arg Val Leu Val  
 515 520 525

Glu Asp Lys Ile Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Tyr  
 530 535 540

Val Tyr Trp Thr Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys  
 545 550 555 560

Arg Ser Ala Glu Arg Glu Val Ile Ile Asp Gln Leu Pro Asp Leu Met  
 565 570 575

Gly Leu Lys Ala Thr Asn Val His Arg Val Ile Gly Ser Asn Pro Cys  
 580 585 590

Ala Glu Glu Asn Gly Gly Cys Ser His Leu Cys Leu Tyr Arg Pro Gln  
 595 600 605

Gly Leu Arg Cys Ala Cys Pro Ile Gly Phe Glu Leu Ile Ser Asp Met  
 610 615 620

Lys Thr Cys Ile Val Pro Glu Ala Phe Leu Leu Phe Ser Arg Arg Ala  
 625 630 635 640

Asp Ile Arg Arg Ile Ser Leu Glu Thr Asn Asn Asn Asn Val Ala Ile  
 645 650 655

Pro Leu Thr Gly Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Thr  
 660 665 670

Asp Asn Arg Ile Tyr Trp Thr Asp Ile Ser Leu Lys Thr Ile Ser Arg  
 675 680 685

Ala Phe Met Asn Gly Ser Ala Leu Glu His Val Val Glu Phe Gly Leu  
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Nonprovisional IP-017.ST25.txt																
690					695					700						
Asp 705	Tyr	Pro	Glu	Gly	Met 710	Ala	Val	Asp	Trp	Leu 715	Gly	Lys	Asn	Leu	Tyr 720	
Trp	Ala	Asp	Thr	Gly 725	Thr	Asn	Arg	Ile	Glu 730	Val	Ser	Lys	Leu	Asp 735	Gly	
Gln	His	Arg	Gln 740	Val	Leu	Val	Trp	Lys 745	Asp	Leu	Asp	Ser	Pro 750	Arg	Ala	
Leu	Ala	Leu 755	Asp	Pro	Ala	Glu	Gly 760	Phe	Met	Tyr	Trp	Thr 765	Glu	Trp	Gly	
Gly	Lys 770	Pro	Lys	Ile	Asp	Arg 775	Ala	Ala	Met	Asp	Gly 780	Ser	Glu	Arg	Thr	
Thr 785	Leu	Val	Pro	Asn	Val 790	Gly	Arg	Ala	Asn	Gly 795	Leu	Thr	Ile	Asp	Tyr 800	
Ala	Lys	Arg	Arg	Leu 805	Tyr	Trp	Thr	Asp	Leu 810	Asp	Thr	Asn	Leu	Ile 815	Glu	
Ser	Ser	Asn	Met 820	Leu	Gly	Leu	Asn	Arg 825	Glu	Val	Ile	Ala	Asp 830	Asp	Leu	
Pro	His	Pro 835	Phe	Gly	Leu	Thr	Gln 840	Tyr	Gln	Asp	Tyr	Ile 845	Tyr	Trp	Thr	
Asp	Trp 850	Ser	Arg	Arg	Ser	Ile 855	Glu	Arg	Ala	Asn	Lys 860	Thr	Ser	Gly	Gln	
Asn 865	Arg	Thr	Ile	Ile	Gln 870	Gly	His	Leu	Asp	Tyr 875	Val	Met	Asp	Ile	Leu 880	
Val	Phe	His	Ser	Ser 885	Arg	Gln	Ser	Gly	Trp 890	Asn	Glu	Cys	Ala	Ser 895	Ser	
Asn	Gly	His	Cys 900	Ser	His	Leu	Cys	Leu 905	Ala	Val	Pro	Val	Gly 910	Gly	Phe	
Val	Cys	Gly 915	Cys	Pro	Ala	His	Tyr 920	Ser	Leu	Asn	Ala	Asp 925	Asn	Arg	Thr	
Cys	Ser 930	Ala	Pro	Thr	Thr	Phe 935	Leu	Leu	Phe	Ser	Gln 940	Lys	Ser	Ala	Ile	
Asn 945	Arg	Met	Val	Ile	Asp 950	Glu	Gln	Gln	Ser	Pro 955	Asp	Ile	Ile	Leu	Pro 960	
Ile	His	Ser	Leu	Arg	Asn	Val	Arg	Ala	Ile	Asp	Tyr	Asp	Pro	Leu	Asp	



975

990

1005

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1080

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1125

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Nonprovisional IP-017.ST25.txt

1220 1225 1230

Leu Val Leu Leu Gln Asp Glu Leu Ser Cys Gly Glu Pro Pro Thr  
1235 1240 1245

Cys Ser Pro Gln Gln Phe Thr Cys Phe Thr Gly Glu Ile Asp Cys  
1250 1255 1260

Ile Pro Val Ala Trp Arg Cys Asp Gly Phe Thr Glu Cys Glu Asp  
1265 1270 1275

His Ser Asp Glu Leu Asn Cys Pro Val Cys Ser Glu Ser Gln Phe  
1280 1285 1290

Gln Cys Ala Ser Gly Gln Cys Ile Asp Gly Ala Leu Arg Cys Asn  
1295 1300 1305

Gly Asp Ala Asn Cys Gln Asp Lys Ser Asp Glu Lys Asn Cys Glu  
1310 1315 1320

Val Leu Cys Leu Ile Asp Gln Phe Arg Cys Ala Asn Gly Gln Cys  
1325 1330 1335

Ile Gly Lys His Lys Lys Cys Asp His Asn Val Asp Cys Ser Asp  
1340 1345 1350

Lys Ser Asp Glu Leu Asp Cys Tyr Pro Thr Glu Glu Pro Ala Pro  
1355 1360 1365

Gln Ala Thr Asn Thr Val Gly Ser Val Ile Gly Val Ile Val Thr  
1370 1375 1380

Ile Phe Val Ser Gly Thr Val Tyr Phe Ile Cys Gln Arg Met Leu  
1385 1390 1395

Cys Pro Arg Met Lys Gly Asp Gly Glu Thr Met Thr Asn Asp Tyr  
1400 1405 1410

Val Val His Gly Pro Ala Ser Val Pro Leu Gly Tyr Val Pro His  
1415 1420 1425

Pro Ser Ser Leu Ser Gly Ser Leu Pro Gly Met Ser Arg Gly Lys  
1430 1435 1440

Ser Met Ile Ser Ser Leu Ser Ile Met Gly Gly Ser Ser Gly Pro  
1445 1450 1455

Pro Tyr Asp Arg Ala His Val Thr Gly Ala Ser Ser Ser Ser Ser  
1460 1465 1470

Ser Ser Thr Lys Gly Thr Tyr Phe Pro Ala Ile Leu Asn Pro Pro

Nonprovisional IP-017.ST25.txt  
 1480 1485

1475  
 Pro Ser Pro Ala Thr Glu Arg Ser His Tyr Thr Met Glu Phe Gly  
 1490 1495 1500  
 Tyr Ser Ser Asn Ser Pro Ser Thr His Arg Ser Tyr Ser Tyr Arg  
 1505 1510 1515  
 Pro Tyr Ser Tyr Arg His Phe Ala Pro Pro Thr Thr Pro Cys Ser  
 1520 1525 1530  
 Thr Asp Val Cys Asp Ser Asp Tyr Ala Pro Ser Arg Arg Met Thr  
 1535 1540 1545  
 Ser Val Ala Thr Ala Lys Gly Tyr Thr Ser Asp Leu Asn Tyr Asp  
 1550 1555 1560  
 Ser Glu Pro Val Pro Pro Pro Pro Thr Pro Arg Ser Gln Tyr Leu  
 1565 1570 1575  
 Ser Ala Glu Glu Asn Tyr Glu Ser Cys Pro Pro Ser Pro Tyr Thr  
 1580 1585 1590  
 Glu Arg Ser Tyr Ser His His Leu Tyr Pro Pro Pro Pro Ser Pro  
 1595 1600 1605  
 Cys Thr Asp Ser Ser  
 1610

<210> 85  
 <211> 996  
 <212> PRT  
 <213> MOUSE

<400> 85

Met Gly Arg Pro Glu Leu Gly Ala Leu Arg Pro Leu Ala Leu Leu Leu  
 1 5 10 15  
 Leu Leu Leu Leu Gln Leu Gln His Leu Ser Ala Ala Asp Pro Leu Leu  
 20 25 30  
 Gly Gly Gln Gly Pro Val Lys Glu Cys Glu Glu Asp Gln Phe Arg Cys  
 35 40 45  
 Arg Asn Glu Arg Cys Ile Pro Leu Val Trp Arg Cys Asp Glu Asp Asn  
 50 55 60  
 Asp Cys Ser Asp Asn Ser Asp Glu Asp Asp Cys Pro Lys Arg Thr Cys  
 65 70 75 80  
 Ala Asp Ser Asp Phe Thr Cys Asp Asn Gly His Cys Ile Pro Glu Arg  
 85 90 95

## Nonprovisional IP-017.ST25.txt

Trp Lys Cys Asp Gly Glu Glu Glu Cys Pro Asp Gly Ser Asp Glu Ser  
 100 105 110  
 Lys Ala Thr Cys Ser Ser Glu Glu Cys Pro Ala Glu Lys Leu Ser Cys  
 115 120 125  
 Gly Pro Thr Ser His Lys Cys Val Pro Ala Ser Trp Arg Cys Asp Gly  
 130 135 140  
 Glu Lys Asp Cys Glu Gly Gly Ala Asp Glu Ala Gly Cys Pro Thr Leu  
 145 150 155 160  
 Cys Ala Pro His Glu Phe Gln Cys Ser Asn Arg Ser Cys Leu Ala Ser  
 165 170 175  
 Val Phe Val Cys Asp Gly Asp Asp Asp Cys Gly Asp Gly Ser Asp Glu  
 180 185 190  
 Arg Gly Cys Ser Asp Pro Ala Cys Pro Pro Arg Glu Phe Arg Cys Gly  
 195 200 205  
 Gly Gly Gly Thr Cys Ile Pro Glu Arg Trp Val Cys Asp Arg Gln Phe  
 210 215 220  
 Asp Cys Glu Asp Arg Ser Asp Glu Ala Ala Glu Leu Cys Gly Arg Ala  
 225 230 235 240  
 Gly Gln Gly Thr Thr Ala Thr Pro Ala Ala Cys Ala Pro Thr Ala Gln  
 245 250 255  
 Phe Thr Cys Arg Ser Gly Glu Cys Ile His Leu Gly Trp Arg Cys Asp  
 260 265 270  
 Gly Asp Arg Asp Cys Lys Asp Lys Ser Asp Glu Ala Asp Cys Ser Pro  
 275 280 285  
 Gly Pro Cys Arg Glu Asn Glu Phe Gln Cys Gly Asp Gly Thr Cys Val  
 290 295 300  
 Leu Ala Ile Lys Arg Cys Asn Gln Glu Arg Asp Cys Pro Asp Gly Ser  
 305 310 315 320  
 Asp Glu Ala Gly Cys Leu Gln Glu Ser Thr Cys Glu Gly Pro Arg Arg  
 325 330 335  
 Phe Gln Cys Lys Ser Gly Glu Cys Val Asp Gly Gly Lys Val Cys Asp  
 340 345 350  
 Asp Gln Arg Asp Cys Arg Asp Trp Ser Asp Glu Pro Gln Lys Val Cys  
 355 360 365

## Nonprovisional IP-017.ST25.txt

Gly Leu Asn Glu Cys Leu His Asn Asn Gly Gly Cys Ser His Ile Cys  
 370 375 380  
 Thr Asp Leu Lys Ile Gly Phe Glu Cys Thr Cys Pro Ala Gly Phe Gln  
 385 390 395 400  
 Leu Leu Asp Gln Lys Thr Cys Gly Asp Ile Asp Glu Cys Gln Asp Pro  
 405 410 415  
 Asp Ala Cys Ser Gln Ile Cys Val Asn Tyr Lys Gly Tyr Phe Lys Cys  
 420 425 430  
 Glu Cys His Pro Gly Tyr Glu Met Asp Thr Leu Thr Lys Asn Cys Lys  
 435 440 445  
 Ala Val Ala Gly Lys Ser Pro Ser Leu Ile Phe Thr Asn Arg His Glu  
 450 455 460  
 Val Arg Arg Ile Asp Leu Val Lys Arg Asp Tyr Ser Arg Leu Ile Pro  
 465 470 475 480  
 Met Leu Lys Asn Val Val Ala Leu Asp Val Glu Val Ala Thr Asn Arg  
 485 490 495  
 Ile Tyr Trp Cys Asp Leu Ser Tyr Arg Lys Ile Tyr Ser Ala His Met  
 500 505 510  
 Asp Lys Ala Ser Ile Pro Asp Glu Gln Val Val Leu Ile Asp Glu Gln  
 515 520 525  
 Leu His Ser Pro Glu Gly Leu Ala Val Asp Trp Val His Lys His Ile  
 530 535 540  
 Tyr Trp Thr Asp Ser Gly Asn Lys Thr Ile Ser Val Ala Thr Thr Asp  
 545 550 555 560  
 Gly Arg Arg Arg Cys Thr Leu Phe Ser Arg Glu Leu Ser Glu Pro Arg  
 565 570 575  
 Ala Ile Ala Val Asp Pro Leu Arg Gly Phe Met Tyr Trp Ser Asp Trp  
 580 585 590  
 Gly Phe Gln Ala Lys Ile Glu Lys Ala Gly Leu Asn Gly Ala Asp Arg  
 595 600 605  
 Gln Thr Leu Val Ser Asp Asn Ile Glu Trp Pro Asn Gly Ile Thr Leu  
 610 615 620  
 Asp Leu Leu Ser Gln Arg Leu Tyr Trp Val Asp Ser Lys Leu His Gln  
 625 630 635 640

## Nonprovisional IP-017.ST25.txt

Leu Ser Ser Ile Asp Phe Asn Gly Gly Asn Arg Lys Met Leu Ile Phe  
 645 650 655  
 Ser Thr Asp Phe Leu Ser His Pro Phe Gly Val Ala Val Phe Glu Asp  
 660 665 670  
 Lys Val Phe Trp Thr Asp Leu Glu Asn Glu Ala Ile Phe Ser Ala Asn  
 675 680 685  
 Arg Leu Asn Gly Leu Glu Ile Ala Ile Leu Ala Glu Asn Leu Asn Asn  
 690 695 700  
 Pro His Asp Ile Val Ile Phe His Glu Leu Lys Gln Pro Lys Ala Ala  
 705 710 715 720  
 Asp Ala Cys Asp Leu Ser Ala Gln Pro Asn Gly Gly Cys Glu Tyr Leu  
 725 730 735  
 Cys Leu Pro Ala Pro Gln Ile Ser Ser His Ser Pro Lys Tyr Thr Cys  
 740 745 750  
 Ala Cys Pro Asp Thr Met Trp Leu Gly Pro Asp Met Lys Arg Cys Tyr  
 755 760 765  
 Arg Ala Pro Gln Ser Thr Ser Thr Thr Thr Leu Ala Ser Ala Met Thr  
 770 775 780  
 Arg Thr Val Pro Ala Thr Thr Arg Ala Pro Gly Thr Thr Ile His Asp  
 785 790 795 800  
 Pro Thr Tyr Gln Asn His Ser Thr Glu Thr Pro Ser Gln Thr Ala Ala  
 805 810 815  
 Ala Pro His Ser Val Asn Val Pro Arg Ala Pro Ser Thr Ser Pro Ser  
 820 825 830  
 Thr Pro Ser Pro Ala Thr Ser Asn His Ser Gln His Tyr Gly Asn Glu  
 835 840 845  
 Gly Ser Gln Met Gly Ser Thr Val Thr Ala Ala Val Ile Gly Val Ile  
 850 855 860  
 Val Pro Ile Val Val Ile Ala Leu Leu Cys Met Ser Gly Tyr Leu Ile  
 865 870 875 880  
 Trp Arg Asn Trp Lys Arg Lys Asn Thr Lys Ser Met Asn Phe Asp Asn  
 885 890 895  
 Pro Val Tyr Arg Lys Thr Thr Glu Glu Glu Glu Asp Glu Leu His  
 900 905 910

## Nonprovisional IP-017.ST25.txt

Ile Gly Arg Thr Ala Gln Ile Gly His Val Tyr Pro Ala Ala Ile Ser  
 915 920 925

Asn Tyr Asp Arg Pro Leu Trp Ala Glu Pro Cys Leu Gly Glu Thr Arg  
 930 935 940

Asp Leu Glu Asp Pro Ala Pro Ala Leu Lys Glu Leu Phe Val Leu Pro  
 945 950 955 960

Gly Glu Pro Arg Ser Gln Leu His Gln Leu Pro Lys Asn Pro Leu Ser  
 965 970 975

Glu Leu Pro Val Val Lys Cys Lys Arg Val Ala Leu Ser Leu Glu Asp  
 980 985 990

Asp Gly Leu Pro  
 995

<210> 86  
 <211> 963  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 86

Met Gly Leu Pro Glu Pro Gly Pro Leu Arg Leu Leu Ala Leu Leu Leu  
 1 5 10 15

Leu Leu Leu Leu Leu Leu Leu Leu Arg Leu Gln His Leu Ala Ala Ala  
 20 25 30

Ala Ala Asp Pro Leu Leu Gly Gly Gln Gly Pro Ala Lys Glu Cys Glu  
 35 40 45

Lys Asp Gln Phe Gln Cys Arg Asn Glu Arg Cys Ile Pro Ser Val Trp  
 50 55 60

Arg Cys Asp Glu Asp Asp Asp Cys Leu Asp His Ser Asp Glu Asp Asp  
 65 70 75 80

Cys Pro Lys Lys Thr Cys Ala Asp Ser Asp Phe Thr Cys Asp Asn Gly  
 85 90 95

His Cys Ile His Glu Arg Trp Lys Cys Asp Gly Glu Glu Glu Cys Pro  
 100 105 110

Asp Gly Ser Asp Glu Ser Glu Ala Thr Cys Thr Lys Gln Val Cys Pro  
 115 120 125

Ala Glu Lys Leu Ser Cys Gly Pro Thr Ser His Lys Cys Val Pro Ala  
 130 135 140

## Nonprovisional IP-017.ST25.txt

Ser Trp Arg Cys Asp Gly Glu Lys Asp Cys Glu Gly Gly Ala Asp Glu  
 145 150 155 160  
 Ala Gly Cys Ala Thr Leu Cys Ala Pro His Glu Phe Gln Cys Gly Asn  
 165 170 175  
 Arg Ser Cys Leu Ala Ala Val Phe Val Cys Asp Gly Asp Asp Asp Cys  
 180 185 190  
 Gly Asp Gly Ser Asp Glu Arg Gly Cys Ala Asp Pro Ala Cys Gly Pro  
 195 200 205  
 Arg Glu Phe Arg Cys Gly Gly Asp Gly Gly Gly Ala Cys Ile Pro Glu  
 210 215 220  
 Arg Trp Val Cys Asp Arg Gln Phe Asp Cys Glu Asp Arg Ser Asp Glu  
 225 230 235 240  
 Ala Ala Glu Leu Cys Gly Arg Pro Gly Pro Gly Ala Thr Ser Ala Pro  
 245 250 255  
 Ala Ala Cys Ala Thr Val Ser Gln Phe Ala Cys Arg Ser Gly Glu Cys  
 260 265 270  
 Val His Leu Gly Trp Arg Cys Asp Gly Asp Arg Asp Cys Lys Asp Lys  
 275 280 285  
 Ser Asp Glu Ala Asp Cys Pro Leu Gly Thr Cys Arg Gly Asp Glu Phe  
 290 295 300  
 Gln Cys Gly Asp Gly Thr Cys Val Leu Ala Ile Lys His Cys Asn Gln  
 305 310 315 320  
 Glu Gln Asp Cys Pro Asp Gly Ser Asp Glu Ala Gly Cys Leu Gln Gly  
 325 330 335  
 Leu Asn Glu Cys Leu His Asn Asn Gly Gly Cys Ser His Ile Cys Thr  
 340 345 350  
 Asp Leu Lys Ile Gly Phe Glu Cys Thr Cys Pro Ala Gly Phe Gln Leu  
 355 360 365  
 Leu Asp Gln Lys Thr Cys Gly Asp Ile Asp Glu Cys Lys Asp Pro Asp  
 370 375 380  
 Ala Cys Ser Gln Ile Cys Val Asn Tyr Lys Gly Tyr Phe Lys Cys Glu  
 385 390 395 400  
 Cys Tyr Pro Gly Tyr Glu Met Asp Leu Leu Thr Lys Asn Cys Lys Ala  
 405 410 415



## Nonprovisional IP-017.ST25.txt

Ala Gly Gly Lys Ser Pro Ser Leu Ile Phe Thr Asn Arg Tyr Glu Val  
 420 425 430  
 Arg Arg Ile Asp Leu Val Lys Arg Asn Tyr Ser Arg Leu Ile Pro Met  
 435 440 445  
 Leu Lys Asn Val Val Ala Leu Asp Val Glu Val Ala Thr Asn Arg Ile  
 450 455 460  
 Tyr Trp Cys Asp Leu Ser Tyr Arg Lys Ile Tyr Ser Ala Tyr Met Asp  
 465 470 475 480  
 Lys Ala Ser Asp Pro Lys Glu Gln Glu Val Leu Ile Asp Glu Gln Leu  
 485 490 495  
 His Ser Pro Glu Gly Leu Ala Val Asp Trp Val His Lys His Ile Tyr  
 500 505 510  
 Trp Thr Asp Ser Gly Asn Lys Thr Ile Ser Val Ala Thr Val Asp Gly  
 515 520 525  
 Gly Arg Arg Arg Thr Leu Phe Ser Arg Asn Leu Ser Glu Pro Arg Ala  
 530 535 540  
 Ile Ala Val Asp Pro Leu Arg Gly Phe Met Tyr Trp Ser Asp Trp Gly  
 545 550 555 560  
 Asp Gln Ala Lys Ile Glu Lys Ser Gly Leu Asn Gly Val Asp Arg Gln  
 565 570 575  
 Thr Leu Val Ser Asp Asn Ile Glu Trp Pro Asn Gly Ile Thr Leu Asp  
 580 585 590  
 Leu Leu Ser Gln Arg Leu Tyr Trp Val Asp Ser Lys Leu His Gln Leu  
 595 600 605  
 Ser Ser Ile Asp Phe Ser Gly Gly Asn Arg Lys Thr Leu Ile Ser Ser  
 610 615 620  
 Thr Asp Phe Leu Ser His Pro Phe Gly Ile Ala Val Phe Glu Asp Lys  
 625 630 635 640  
 Val Phe Trp Thr Asp Leu Glu Asn Glu Ala Ile Phe Ser Ala Asn Arg  
 645 650 655  
 Leu Asn Gly Leu Glu Ile Ser Ile Leu Ala Glu Asn Leu Asn Asn Pro  
 660 665 670  
 His Asp Ile Val Ile Phe His Glu Leu Lys Gln Pro Arg Ala Pro Asp  
 675 680 685

## Nonprovisional IP-017.ST25.txt

Ala Cys Glu Leu Ser Val Gln Pro Asn Gly Gly Cys Glu Tyr Leu Cys  
 690 695 700  
 Leu Pro Ala Pro Gln Ile Ser Ser His Ser Pro Lys Tyr Thr Cys Ala  
 705 710 715 720  
 Cys Pro Asp Thr Met Trp Leu Gly Pro Asp Met Lys Arg Cys Tyr Arg  
 725 730 735  
 Ala Pro Gln Ser Thr Ser Thr Thr Thr Leu Ala Ser Thr Met Thr Arg  
 740 745 750  
 Thr Val Pro Ala Thr Thr Arg Ala Pro Gly Thr Thr Val His Arg Ser  
 755 760 765  
 Thr Tyr Gln Asn His Ser Thr Glu Thr Pro Ser Leu Thr Ala Ala Val  
 770 775 780  
 Pro Ser Ser Val Ser Val Pro Arg Ala Pro Ser Ile Ser Pro Ser Thr  
 785 790 795 800  
 Leu Ser Pro Ala Thr Ser Asn His Ser Gln His Tyr Ala Asn Glu Asp  
 805 810 815  
 Ser Lys Met Gly Ser Thr Val Thr Ala Ala Val Ile Gly Ile Ile Val  
 820 825 830  
 Pro Ile Val Val Ile Ala Leu Leu Cys Met Ser Gly Tyr Leu Ile Trp  
 835 840 845  
 Arg Asn Trp Lys Arg Lys Asn Thr Lys Ser Met Asn Phe Asp Asn Pro  
 850 855 860  
 Val Tyr Arg Lys Thr Thr Glu Glu Glu Asp Glu Asp Glu Leu His Ile  
 865 870 875 880  
 Gly Arg Thr Ala Gln Ile Gly His Val Tyr Pro Ala Ala Ile Ser Ser  
 885 890 895  
 Phe Asp Arg Pro Leu Trp Ala Glu Pro Cys Leu Gly Glu Thr Arg Glu  
 900 905 910  
 Pro Glu Asp Pro Ala Pro Ala Leu Lys Glu Leu Phe Val Leu Pro Gly  
 915 920 925  
 Glu Pro Arg Ser Gln Leu His Gln Leu Pro Lys Asn Pro Leu Ser Glu  
 930 935 940  
 Leu Pro Val Val Lys Ser Lys Arg Val Ala Leu Ser Leu Glu Asp Asp  
 945 950 955 960

## Nonprovisional IP-017.ST25.txt

Gly Leu Pro

<210> 87  
 <211> 713  
 <212> PRT  
 <213> MOUSE

&lt;400&gt; 87

Met Leu Ser Ala Leu Pro Leu Leu Phe Leu Leu Leu Gly Gly Ala Leu  
 1 5 10 15

Ala Arg Pro Asp Arg Ile Thr Phe Pro Arg Ser Ala Cys Glu Ala Pro  
 20 25 30

Pro Ala Val Leu Ser Glu Val Gln Gly Thr Leu Gln Arg Pro Leu Gly  
 35 40 45

Arg Asp Ser Arg Ser Ser Pro Ala Asn Cys Thr Trp Val Ile Leu Gly  
 50 55 60

Ser Lys Asp Gln Thr Val Thr Val Arg Phe Gln Lys Leu His Leu Ala  
 65 70 75 80

Cys Gly Ser Glu His Leu Ile Leu His Ser Pro Leu Gln Pro Pro Ile  
 85 90 95

Ser Leu Cys Glu Ala Pro Ser Gly Pro Leu Gln Leu Pro Gly Gly Asn  
 100 105 110

Val Thr Ile Thr Tyr Ser Tyr Ala Gly Ala Arg Ala Pro Met Gly Gln  
 115 120 125

Gly Phe Leu Leu Thr Tyr Ser Gln Asp Trp Leu Leu Cys Leu Gln Glu  
 130 135 140

Glu Phe Gln Cys Leu Asn His Arg Cys Ile Pro Ala Ala Gln Arg Cys  
 145 150 155 160

Asp Gly Ile Asp Ala Cys Gly Asp Gly Ser Asp Glu Ala Gly Cys Ser  
 165 170 175

Ser Asp Pro Phe Pro Asn Leu Asn Pro Ala Pro Ala Pro Thr Leu Ala  
 180 185 190

Cys Asn Leu Thr Leu Glu Asp Phe Tyr Gly Val Phe Ser Ser Pro Gly  
 195 200 205

Tyr Ser His Leu Ala Ser Val Ser His Pro Gln Ser Cys Leu Trp Leu  
 210 215 220

## Nonprovisional IP-017.ST25.txt

Leu Asp Pro His Asp Gly Arg Arg Leu Ala Val Arg Phe Thr Ala Leu  
 225 230 235 240  
 Asp Leu Ser Tyr Gly Asp Ala Val His Val Tyr Asp Gly Ala Gly Pro  
 245 250 255  
 Pro Glu Thr Pro Arg Leu Leu Arg Ser Leu Thr His Phe Ser Asn Gly  
 260 265 270  
 Lys Ala Val Thr Val Glu Thr Leu Ser Gly Gln Ala Val Val Ser Tyr  
 275 280 285  
 His Thr Val Ala Trp Ser Ser Gly Arg Gly Phe Asn Ala Thr Tyr His  
 290 295 300  
 Val Arg Gly Tyr Cys Leu Pro Trp Asp Arg Pro Cys Gly Leu Gly Ser  
 305 310 315 320  
 Gly Leu Gly Ala Ser Glu Asn Leu Gly Glu Arg Cys Tyr Ser Glu Ala  
 325 330 335  
 Gln Arg Cys Asp Gly Ser Trp Asp Cys Ala Asp Gly Thr Asp Glu Glu  
 340 345 350  
 Gly Cys Pro Gly Cys Pro Pro Gly His Phe Pro Cys Gly Ala Ala Gly  
 355 360 365  
 Thr Pro Gly Ala Thr Ala Cys Tyr Leu Pro Ala Asp Arg Cys Asn Tyr  
 370 375 380  
 Gln Thr Phe Cys Ala Asp Gly Ala Asp Glu Arg Arg Cys Arg His Cys  
 385 390 395 400  
 Gln Pro Gly Asn Phe Arg Cys Arg Asp Glu Lys Cys Val Tyr Glu Thr  
 405 410 415  
 Trp Val Cys Asp Gly Gln Pro Asp Cys Thr Asp Gly Ser Asp Glu Trp  
 420 425 430  
 Asp Cys Ser Tyr Ala Leu Pro Arg Lys Val Ile Thr Ala Ala Val Ile  
 435 440 445  
 Gly Ser Leu Val Cys Gly Leu Leu Leu Val Ile Ala Leu Gly Cys Thr  
 450 455 460  
 Cys Lys Leu Tyr Ala Ile Arg Thr Gln Glu Tyr Ser Ile Phe Ala Pro  
 465 470 475 480  
 Leu Ser Arg Met Glu Ala Glu Ile Val Gln Gln Gln Ala Pro Pro Ser  
 485 490 495

Nonprovisional IP-017.ST25.txt

Tyr Gly Gln Leu Ile Ala Gln Gly Ala Ile Pro Pro Val Glu Asp Phe  
 500 505 510

Pro Thr Glu Asn Pro Asn Asp Asn Ser Val Leu Gly Asn Leu Arg Ser  
 515 520 525

Leu Leu Gln Ile Leu Arg Gln Asp Met Thr Pro Gly Gly Thr Ser Gly  
 530 535 540

Gly Arg Arg Arg Gln Arg Gly Arg Ser Val Arg Arg Leu Val Arg Arg  
 545 550 555 560

Leu Arg Arg Trp Gly Leu Leu Pro Arg Thr Asn Thr Pro Ala Arg Ala  
 565 570 575

Pro Glu Thr Arg Ser Gln Val Thr Pro Ser Val Pro Ser Glu Ala Leu  
 580 585 590

Asp Asp Ser Thr Gly His Ala Cys Glu Gly Gly Ala Val Gly Gly Gln  
 595 600 605

Asp Gly Glu Gln Ala Pro Pro Leu Pro Ile Lys Thr Pro Ile Pro Thr  
 610 615 620

Pro Ser Thr Leu Pro Ala Leu Ala Thr Val Ser Glu Thr Pro Gly Pro  
 625 630 635 640

Leu Pro Ser Val Pro Val Glu Ser Ser Leu Leu Ser Gly Val Val Gln  
 645 650 655

Val Leu Arg Gly Arg Leu Leu Pro Ser Leu Trp Ser Pro Gly Pro Thr  
 660 665 670

Trp Thr Gln Thr Gly Thr His Thr Thr Val Leu Ser Pro Glu Asp Glu  
 675 680 685

Asp Asp Val Leu Leu Leu Pro Leu Ala Glu Pro Glu Val Trp Val Val  
 690 695 700

Glu Ala Glu Asp Glu Pro Leu Leu Ala  
 705 710

<210> 88  
 <211> 713  
 <212> PRT  
 <213> MOUSE

<400> 88

Met Leu Ser Ala Leu Pro Leu Leu Phe Leu Leu Leu Gly Gly Ala Leu  
 1 5 10 15

Ala Arg Pro Asp Arg Ile Thr Phe Pro Arg Ser Ala Cys Glu Ala Pro  
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Nonprovisional IP-017.ST25.txt

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25

30

Pro Ala Val<sub>35</sub> Leu Ser Glu Val<sub>40</sub> Gln Gly Thr Leu Gln Arg<sub>45</sub> Pro Leu Gly  
 Arg Asp<sub>50</sub> Ser Arg Ser Ser Pro<sub>55</sub> Ala Asn Cys Thr Trp<sub>60</sub> Val Ile Leu Gly  
 Ser Lys Asp Gln Thr Val<sub>70</sub> Thr Val Arg Phe Gln<sub>75</sub> Lys Leu His Leu Ala<sub>80</sub>  
 Cys Gly Ser Glu His<sub>85</sub> Leu Ile Leu His Ser<sub>90</sub> Pro Leu Gln Pro Pro<sub>95</sub> Ile  
 Ser Leu Cys Glu<sub>100</sub> Ala Pro Ser Gly Pro<sub>105</sub> Leu Gln Leu Pro Gly<sub>110</sub> Gly Asn  
 Val Thr Ile<sub>115</sub> Thr Tyr Ser Tyr Ala<sub>120</sub> Gly Ala Arg Ala Pro<sub>125</sub> Met Gly Gln  
 Gly Phe<sub>130</sub> Leu Leu Thr Tyr Ser<sub>135</sub> Gln Asp Trp Leu Leu<sub>140</sub> Cys Leu Gln Glu  
 Glu Phe<sub>145</sub> Gln Cys Leu Asn<sub>150</sub> His Arg Cys Ile Pro<sub>155</sub> Ala Ala Gln Arg Cys<sub>160</sub>  
 Asp Gly Ile Asp Ala<sub>165</sub> Cys Gly Asp Gly Ser<sub>170</sub> Asp Glu Ala Gly Cys<sub>175</sub> Ser  
 Ser Asp Pro Phe<sub>180</sub> Pro Asn Leu Asn Pro<sub>185</sub> Ala Pro Ala Pro Thr<sub>190</sub> Leu Ala  
 Cys Asn Leu<sub>195</sub> Thr Leu Glu Asp Phe<sub>200</sub> Tyr Gly Val Phe Ser<sub>205</sub> Ser Pro Gly  
 Tyr Ser<sub>210</sub> His Leu Ala Ser Val<sub>215</sub> Ser His Pro Gln Ser<sub>220</sub> Cys Leu Trp Leu  
 Leu Asp Pro His Asp Gly<sub>230</sub> Arg Arg Leu Ala Val<sub>235</sub> Arg Phe Thr Ala Leu<sub>240</sub>  
 Asp Leu Ser Tyr Gly<sub>245</sub> Asp Ala Val His Val<sub>250</sub> Tyr Asp Gly Ala Gly<sub>255</sub> Pro  
 Pro Glu Thr Pro<sub>260</sub> Arg Leu Leu Arg Ser<sub>265</sub> Leu Thr His Phe Ser<sub>270</sub> Asn Gly  
 Lys Ala Val<sub>275</sub> Thr Val Glu Thr Leu Ser Gly Gln Ala Val<sub>285</sub> Val Ser Tyr  
 His Thr Val Ala Trp Ser Ser Gly Arg Gly Phe Asn Ala Thr Tyr His  
 Page 282

Nonprovisional IP-017.ST25.txt  
295 300

290

Val Arg Gly Tyr Cys Leu Pro Trp Asp Arg Pro Cys Gly Leu Gly Ser  
 305 310 315 320  
 Gly Leu Gly Ala Ser Glu Asn Leu Gly Glu Arg Cys Tyr Ser Glu Ala  
 325 330 335  
 Gln Arg Cys Asp Gly Ser Trp Asp Cys Ala Asp Gly Thr Asp Glu Glu  
 340 345 350  
 Gly Cys Pro Gly Cys Pro Pro Gly His Phe Pro Cys Gly Ala Ala Gly  
 355 360 365  
 Thr Pro Gly Ala Thr Ala Cys Tyr Leu Pro Ala Asp Arg Cys Asn Tyr  
 370 375 380  
 Gln Thr Phe Cys Ala Asp Gly Ala Asp Glu Arg Arg Cys Arg His Cys  
 385 390 395 400  
 Gln Pro Gly Asn Phe Arg Cys Arg Asp Glu Lys Cys Val Tyr Glu Thr  
 405 410 415  
 Trp Val Cys Asp Gly Gln Pro Asp Cys Thr Asp Gly Ser Asp Glu Trp  
 420 425 430  
 Asp Cys Ser Tyr Ala Leu Pro Arg Lys Val Ile Thr Ala Ala Val Ile  
 435 440 445  
 Gly Ser Leu Val Cys Gly Leu Leu Leu Val Ile Ala Leu Gly Cys Thr  
 450 455 460  
 Cys Lys Leu Tyr Ala Ile Arg Thr Gln Glu Tyr Ser Ile Phe Ala Pro  
 465 470 475 480  
 Leu Ser Arg Met Glu Ala Glu Ile Val Gln Gln Gln Ala Pro Pro Ser  
 485 490 495  
 Tyr Gly Gln Leu Ile Ala Gln Gly Ala Ile Pro Pro Val Glu Asp Phe  
 500 505 510  
 Pro Thr Glu Asn Pro Asn Asp Asn Ser Val Leu Gly Asn Leu Arg Ser  
 515 520 525  
 Leu Leu Gln Ile Leu Arg Gln Asp Met Thr Pro Gly Gly Thr Ser Gly  
 530 535 540  
 Gly Arg Arg Arg Gln Arg Gly Arg Ser Ile Arg Arg Leu Val Arg Arg  
 545 550 555 560  
 Leu Arg Arg Trp Gly Leu Leu Pro Arg Thr Asn Thr Pro Ala Arg Ala

Nonprovisional IP-017.ST25.txt

565

570

575

Pro Glu Thr Arg Ser Gln Val Thr Pro Ser Val Pro Ser Glu Ala Leu  
 580 585 590

Asp Asp Ser Thr Gly Gln Ala Cys Glu Gly Gly Ala Val Gly Gly Gln  
 595 600 605

Asp Gly Glu Gln Ala Pro Pro Leu Pro Ile Lys Thr Pro Ile Pro Thr  
 610 615 620

Pro Ser Thr Leu Pro Ala Leu Ala Thr Val Ser Glu Pro Pro Gly Pro  
 625 630 635 640

Leu Pro Ser Val Pro Val Glu Ser Ser Leu Leu Ser Gly Val Val Gln  
 645 650 655

Val Leu Arg Gly Arg Leu Leu Pro Ser Leu Trp Ser Pro Gly Pro Thr  
 660 665 670

Trp Thr Gln Thr Gly Thr His Thr Thr Val Leu Ser Pro Glu Asp Glu  
 675 680 685

Asp Asp Val Leu Leu Leu Pro Leu Ala Glu Pro Glu Val Trp Val Val  
 690 695 700

Glu Ala Glu Asp Glu Pro Leu Leu Ala  
 705 710

<210> 89  
 <211> 2214  
 <212> PRT  
 <213> HOMO SAPIENS

<400> 89

Met Ala Thr Arg Ser Ser Arg Arg Glu Ser Arg Leu Pro Phe Leu Phe  
 1 5 10 15

Thr Leu Val Ala Leu Leu Pro Pro Gly Ala Leu Cys Glu Val Trp Thr  
 20 25 30

Gln Arg Leu His Gly Gly Ser Ala Pro Leu Pro Gln Asp Arg Gly Phe  
 35 40 45

Leu Val Val Gln Gly Asp Pro Arg Glu Leu Arg Leu Trp Ala Arg Gly  
 50 55 60

Asp Ala Arg Gly Ala Ser Arg Ala Asp Glu Lys Pro Leu Arg Arg Lys  
 65 70 75 80

Arg Ser Ala Ala Leu Gln Pro Glu Pro Ile Lys Val Tyr Gly Gln Val  
 85 90 95



## Nonprovisional IP-017.ST25.txt

Ser Leu Asn Asp Ser His Asn Gln Met Val Val His Trp Ala Gly Glu  
 100 105 110  
 Lys Ser Asn Val Ile Val Ala Leu Ala Arg Asp Ser Leu Ala Leu Ala  
 115 120 125  
 Arg Pro Lys Ser Ser Asp Val Tyr Val Ser Tyr Asp Tyr Gly Lys Ser  
 130 135 140  
 Phe Lys Lys Ile Ser Asp Lys Leu Asn Phe Gly Leu Gly Asn Arg Ser  
 145 150 155 160  
 Glu Ala Val Ile Ala Gln Phe Tyr His Ser Pro Ala Asp Asn Lys Arg  
 165 170 175  
 Tyr Ile Phe Ala Asp Ala Tyr Ala Gln Tyr Leu Trp Ile Thr Phe Asp  
 180 185 190  
 Phe Cys Asn Thr Leu Gln Gly Phe Ser Ile Pro Phe Arg Ala Ala Asp  
 195 200 205  
 Leu Leu Leu His Ser Lys Ala Ser Asn Leu Leu Leu Gly Phe Asp Arg  
 210 215 220  
 Ser His Pro Asn Lys Gln Leu Trp Lys Ser Asp Asp Phe Gly Gln Thr  
 225 230 235 240  
 Trp Ile Met Ile Gln Glu His Val Lys Ser Phe Ser Trp Gly Ile Asp  
 245 250 255  
 Pro Tyr Asp Lys Pro Asn Thr Ile Tyr Ile Glu Arg His Glu Pro Ser  
 260 265 270  
 Gly Tyr Ser Thr Val Phe Arg Ser Thr Asp Phe Phe Gln Ser Arg Glu  
 275 280 285  
 Asn Gln Glu Val Ile Leu Glu Glu Val Arg Asp Phe Gln Leu Arg Asp  
 290 295 300  
 Lys Tyr Met Phe Ala Thr Lys Val Val His Leu Leu Gly Ser Glu Gln  
 305 310 315 320  
 Gln Ser Ser Val Gln Leu Trp Val Ser Phe Gly Arg Lys Pro Met Arg  
 325 330 335  
 Ala Ala Gln Phe Val Thr Arg His Pro Ile Asn Glu Tyr Tyr Ile Ala  
 340 345 350  
 Asp Ala Ser Glu Asp Gln Val Phe Val Cys Val Ser His Ser Asn Asn  
 355 360 365

## Nonprovisional IP-017.ST25.txt

Arg Thr Asn Leu Tyr Ile Ser Glu Ala Glu Gly Leu Lys Phe Ser Leu  
 370 375 380  
 Ser Leu Glu Asn Val Leu Tyr Tyr Ser Pro Gly Gly Ala Gly Ser Asp  
 385 390 395 400  
 Thr Leu Val Arg Tyr Phe Ala Asn Glu Pro Phe Ala Asp Phe His Arg  
 405 410 415  
 Val Glu Gly Leu Gln Gly Val Tyr Ile Ala Thr Leu Ile Asn Gly Ser  
 420 425 430  
 Met Asn Glu Glu Asn Met Arg Ser Val Ile Thr Phe Asp Lys Gly Gly  
 435 440 445  
 Thr Trp Glu Phe Leu Gln Ala Pro Ala Phe Thr Gly Tyr Gly Glu Lys  
 450 455 460  
 Ile Asn Cys Glu Leu Ser Gln Gly Cys Ser Leu His Leu Ala Gln Arg  
 465 470 475 480  
 Leu Ser Gln Leu Leu Asn Leu Gln Leu Arg Arg Met Pro Ile Leu Ser  
 485 490 495  
 Lys Glu Ser Ala Pro Gly Leu Ile Ile Ala Thr Gly Ser Val Gly Lys  
 500 505 510  
 Asn Leu Ala Ser Lys Thr Asn Val Tyr Ile Ser Ser Ser Ala Gly Ala  
 515 520 525  
 Arg Trp Arg Glu Ala Leu Pro Gly Pro His Tyr Tyr Thr Trp Gly Asp  
 530 535 540  
 His Gly Gly Ile Ile Thr Ala Ile Ala Gln Gly Met Glu Thr Asn Glu  
 545 550 555 560  
 Leu Lys Tyr Ser Thr Asn Glu Gly Glu Thr Trp Lys Thr Phe Ile Phe  
 565 570 575  
 Ser Glu Lys Pro Val Phe Val Tyr Gly Leu Leu Thr Glu Pro Gly Glu  
 580 585 590  
 Lys Ser Thr Val Phe Thr Ile Phe Gly Ser Asn Lys Glu Asn Val His  
 595 600 605  
 Ser Trp Leu Ile Leu Gln Val Asn Ala Thr Asp Ala Leu Gly Val Pro  
 610 615 620  
 Cys Thr Glu Asn Asp Tyr Lys Leu Trp Ser Pro Ser Asp Glu Arg Gly  
 625 630 635 640

## Nonprovisional IP-017.ST25.txt

Asn Glu Cys Leu Leu Gly His Lys Thr Val Phe Lys Arg Arg Thr Pro  
 645 650 655  
 His Ala Thr Cys Phe Asn Gly Glu Asp Phe Asp Arg Pro Val Val Val  
 660 665 670  
 Ser Asn Cys Ser Cys Thr Arg Glu Asp Tyr Glu Cys Asp Phe Gly Phe  
 675 680 685  
 Lys Met Ser Glu Asp Leu Ser Leu Glu Val Cys Val Pro Asp Pro Glu  
 690 695 700  
 Phe Ser Gly Lys Ser Tyr Ser Pro Pro Val Pro Cys Pro Val Gly Ser  
 705 710 715 720  
 Thr Tyr Arg Arg Thr Arg Gly Tyr Arg Lys Ile Ser Gly Asp Thr Cys  
 725 730 735  
 Ser Gly Gly Asp Val Glu Ala Arg Leu Glu Gly Glu Leu Val Pro Cys  
 740 745 750  
 Pro Leu Ala Glu Glu Asn Glu Phe Ile Leu Tyr Ala Val Arg Lys Ser  
 755 760 765  
 Ile Tyr Arg Tyr Asp Leu Ala Ser Gly Ala Thr Glu Gln Leu Pro Leu  
 770 775 780  
 Thr Gly Leu Arg Ala Ala Val Ala Leu Asp Phe Asp Tyr Glu His Asn  
 785 790 795 800  
 Cys Leu Tyr Trp Ser Asp Leu Ala Leu Asp Val Ile Gln Arg Leu Cys  
 805 810 815  
 Leu Asn Gly Ser Thr Gly Gln Glu Val Ile Ile Asn Ser Gly Leu Glu  
 820 825 830  
 Thr Val Glu Ala Leu Ala Phe Glu Pro Leu Ser Gln Leu Leu Tyr Trp  
 835 840 845  
 Val Asp Ala Gly Phe Lys Lys Ile Glu Val Ala Asn Pro Asp Gly Asp  
 850 855 860  
 Phe Arg Leu Thr Ile Val Asn Ser Ser Val Leu Asp Arg Pro Arg Ala  
 865 870 875 880  
 Leu Val Leu Val Pro Gln Glu Gly Val Met Phe Trp Thr Asp Trp Gly  
 885 890 895  
 Asp Leu Lys Pro Gly Ile Tyr Arg Ser Asn Met Asp Gly Ser Ala Ala  
 900 905 910

## Nonprovisional IP-017.ST25.txt

Tyr His Leu Val Ser Glu Asp Val Lys Trp Pro Asn Gly Ile Ser Val  
 915 920 925  
 Asp Asp Gln Trp Ile Tyr Trp Thr Asp Ala Tyr Leu Glu Cys Ile Glu  
 930 935 940  
 Arg Ile Thr Phe Ser Gly Gln Gln Arg Ser Val Ile Leu Asp Asn Leu  
 945 950 955 960  
 Pro His Pro Tyr Ala Ile Ala Val Phe Lys Asn Glu Ile Tyr Trp Asp  
 965 970 975  
 Asp Trp Ser Gln Leu Ser Ile Phe Arg Ala Ser Lys Tyr Ser Gly Ser  
 980 985 990  
 Gln Met Glu Ile Leu Ala Asn Gln Leu Thr Gly Leu Met Asp Met Lys  
 995 1000 1005  
 Ile Phe Tyr Lys Gly Lys Asn Thr Gly Ser Asn Ala Cys Val Pro  
 1010 1015 1020  
 Arg Pro Cys Ser Leu Leu Cys Leu Pro Lys Ala Asn Asn Ser Arg  
 1025 1030 1035  
 Ser Cys Arg Cys Pro Glu Asp Val Ser Ser Ser Val Leu Pro Ser  
 1040 1045 1050  
 Gly Asp Leu Met Cys Asp Cys Pro Gln Gly Tyr Gln Leu Lys Asn  
 1055 1060 1065  
 Asn Thr Cys Val Lys Glu Glu Asn Thr Cys Leu Arg Asn Gln Tyr  
 1070 1075 1080  
 Arg Cys Ser Asn Gly Asn Cys Ile Asn Ser Ile Trp Trp Cys Asp  
 1085 1090 1095  
 Phe Asp Asn Asp Cys Gly Asp Met Ser Asp Glu Arg Asn Cys Pro  
 1100 1105 1110  
 Thr Thr Ile Cys Asp Leu Asp Thr Gln Phe Arg Cys Gln Glu Ser  
 1115 1120 1125  
 Gly Thr Cys Ile Pro Leu Ser Tyr Lys Cys Asp Leu Glu Asp Asp  
 1130 1135 1140  
 Cys Gly Asp Asn Ser Asp Glu Ser His Cys Glu Met His Gln Cys  
 1145 1150 1155  
 Arg Ser Asp Glu Tyr Asn Cys Ser Ser Gly Met Cys Ile Arg Ser  
 1160 1165 1170

## Nonprovisional IP-017.ST25.txt

Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Arg Asp Trp Ser Asp  
 1175 1180 1185  
 Glu Ala Asn Cys Thr Ala Ile Tyr His Thr Cys Glu Ala Ser Asn  
 1190 1195 1200  
 Phe Gln Cys Arg Asn Gly His Cys Ile Pro Gln Arg Trp Ala Cys  
 1205 1210 1215  
 Asp Gly Asp Thr Asp Cys Gln Asp Gly Ser Asp Glu Asp Pro Val  
 1220 1225 1230  
 Asn Cys Glu Lys Lys Cys Asn Gly Phe Arg Cys Pro Asn Gly Thr  
 1235 1240 1245  
 Cys Ile Pro Ser Ser Lys His Cys Asp Gly Leu Arg Asp Cys Ser  
 1250 1255 1260  
 Asp Gly Ser Asp Glu Gln His Cys Glu Pro Leu Cys Thr His Phe  
 1265 1270 1275  
 Met Asp Phe Val Cys Lys Asn Arg Gln Gln Cys Leu Phe His Ser  
 1280 1285 1290  
 Met Val Cys Asp Gly Ile Ile Gln Cys Arg Asp Gly Ser Asp Glu  
 1295 1300 1305  
 Asp Ala Ala Phe Ala Gly Cys Ser Gln Asp Pro Glu Phe His Lys  
 1310 1315 1320  
 Val Cys Asp Glu Phe Gly Phe Gln Cys Gln Asn Gly Val Cys Ile  
 1325 1330 1335  
 Ser Leu Ile Trp Lys Cys Asp Gly Met Asp Asp Cys Gly Asp Tyr  
 1340 1345 1350  
 Ser Asp Glu Ala Asn Cys Glu Asn Pro Thr Glu Ala Pro Asn Cys  
 1355 1360 1365  
 Ser Arg Tyr Phe Gln Phe Arg Cys Glu Asn Gly His Cys Ile Pro  
 1370 1375 1380  
 Asn Arg Trp Lys Cys Asp Arg Glu Asn Asp Cys Gly Asp Trp Ser  
 1385 1390 1395  
 Asp Glu Lys Asp Cys Gly Asp Ser His Ile Leu Pro Phe Ser Thr  
 1400 1405 1410  
 Pro Gly Pro Ser Thr Cys Leu Pro Asn Tyr Tyr Arg Cys Ser Ser  
 1415 1420 1425

## Nonprovisional IP-017.ST25.txt

Gly Thr Cys Val Met Asp Thr Trp Val Cys Asp Gly Tyr Arg Asp  
 1430 1435 1440  
 Cys Ala Asp Gly Ser Asp Glu Glu Ala Cys Pro Leu Leu Ala Asn  
 1445 1450 1455  
 Val Thr Ala Ala Ser Thr Pro Thr Gln Leu Gly Arg Cys Asp Arg  
 1460 1465 1470  
 Phe Glu Phe Glu Cys His Gln Pro Lys Thr Cys Ile Pro Asn Trp  
 1475 1480 1485  
 Lys Arg Cys Asp Gly His Gln Asp Cys Gln Asp Gly Arg Asp Glu  
 1490 1495 1500  
 Ala Asn Cys Pro Thr His Ser Thr Leu Thr Cys Met Ser Arg Glu  
 1505 1510 1515  
 Phe Gln Cys Glu Asp Gly Glu Ala Cys Ile Val Leu Ser Glu Arg  
 1520 1525 1530  
 Cys Asp Gly Phe Leu Asp Cys Ser Asp Glu Ser Asp Glu Lys Ala  
 1535 1540 1545  
 Cys Ser Asp Glu Leu Thr Val Tyr Lys Val Gln Asn Leu Gln Trp  
 1550 1555 1560  
 Thr Ala Asp Phe Ser Gly Asp Val Thr Leu Thr Trp Met Arg Pro  
 1565 1570 1575  
 Lys Lys Met Pro Ser Ala Ser Cys Val Tyr Asn Val Tyr Tyr Arg  
 1580 1585 1590  
 Val Val Gly Glu Ser Ile Trp Lys Thr Leu Glu Thr His Ser Asn  
 1595 1600 1605  
 Lys Thr Asn Thr Val Leu Lys Val Leu Lys Pro Asp Thr Thr Tyr  
 1610 1615 1620  
 Gln Val Lys Val Gln Val Gln Cys Leu Ser Lys Ala His Asn Thr  
 1625 1630 1635  
 Asn Asp Phe Val Thr Leu Arg Thr Pro Glu Gly Leu Pro Asp Ala  
 1640 1645 1650  
 Pro Arg Asn Leu Gln Leu Ser Leu Pro Arg Glu Ala Glu Gly Val  
 1655 1660 1665  
 Ile Val Gly His Trp Ala Pro Pro Ile His Thr His Gly Leu Ile  
 1670 1675 1680

## Nonprovisional IP-017.ST25.txt

Arg Glu Tyr Ile Val Glu Tyr Ser Arg Ser Gly Ser Lys Met Trp  
 1685 1690 1695  
 Ala Ser Gln Arg Ala Ala Ser Asn Phe Thr Glu Ile Lys Asn Leu  
 1700 1705 1710  
 Leu Val Asn Thr Leu Tyr Thr Val Arg Val Ala Ala Val Thr Ser  
 1715 1720 1725  
 Arg Gly Ile Gly Asn Trp Ser Asp Ser Lys Ser Ile Thr Thr Ile  
 1730 1735 1740  
 Lys Gly Lys Val Ile Pro Pro Pro Asp Ile His Ile Asp Ser Tyr  
 1745 1750 1755  
 Gly Glu Asn Tyr Leu Ser Phe Thr Leu Thr Met Glu Ser Asp Ile  
 1760 1765 1770  
 Lys Val Asn Gly Tyr Val Val Asn Leu Phe Trp Ala Phe Asp Thr  
 1775 1780 1785  
 His Lys Gln Glu Arg Arg Thr Leu Asn Phe Arg Gly Ser Ile Leu  
 1790 1795 1800  
 Ser His Lys Val Gly Asn Leu Thr Ala His Thr Ser Tyr Glu Ile  
 1805 1810 1815  
 Ser Ala Trp Ala Lys Thr Asp Leu Gly Asp Ser Pro Leu Ala Phe  
 1820 1825 1830  
 Glu His Val Met Thr Arg Gly Val Arg Pro Pro Ala Pro Ser Leu  
 1835 1840 1845  
 Lys Ala Lys Ala Ile Asn Gln Thr Ala Val Glu Cys Thr Trp Thr  
 1850 1855 1860  
 Gly Pro Arg Asn Val Val Tyr Gly Ile Phe Tyr Ala Thr Ser Phe  
 1865 1870 1875  
 Leu Asp Leu Tyr Arg Asn Pro Lys Ser Leu Thr Thr Ser Leu His  
 1880 1885 1890  
 Asn Lys Thr Val Ile Val Ser Lys Asp Glu Gln Tyr Leu Phe Leu  
 1895 1900 1905  
 Val Arg Val Val Val Pro Tyr Gln Gly Pro Ser Ser Asp Tyr Val  
 1910 1915 1920  
 Val Val Lys Met Ile Pro Asp Ser Arg Leu Pro Pro Arg His Leu  
 1925 1930 1935

## Nonprovisional IP-017.ST25.txt

His Val Val His Thr Gly Lys Thr Ser Val Val Ile Lys Trp Glu  
 1940 1945 1950  
 Ser Pro Tyr Asp Ser Pro Asp Gln Asp Leu Leu Tyr Ala Ile Ala  
 1955 1960 1965  
 Val Lys Asp Leu Ile Arg Lys Thr Asp Arg Ser Tyr Lys Val Lys  
 1970 1975 1980  
 Ser Arg Asn Ser Thr Val Glu Tyr Thr Leu Asn Lys Leu Glu Pro  
 1985 1990 1995  
 Gly Gly Lys Tyr His Ile Ile Val Gln Leu Gly Asn Met Ser Lys  
 2000 2005 2010  
 Asp Ser Ser Ile Lys Ile Thr Thr Val Ser Leu Ser Ala Pro Asp  
 2015 2020 2025  
 Ala Leu Lys Ile Ile Thr Glu Asn Asp His Val Leu Leu Phe Trp  
 2030 2035 2040  
 Lys Ser Leu Ala Leu Lys Glu Lys His Phe Asn Glu Ser Arg Gly  
 2045 2050 2055  
 Tyr Glu Ile His Met Phe Asp Ser Ala Met Asn Ile Thr Ala Tyr  
 2060 2065 2070  
 Leu Gly Asn Thr Thr Asp Asn Phe Phe Lys Ile Ser Asn Leu Lys  
 2075 2080 2085  
 Met Gly His Asn Tyr Thr Phe Thr Val Gln Ala Arg Cys Leu Phe  
 2090 2095 2100  
 Gly Asn Gln Ile Cys Gly Glu Pro Ala Ile Leu Leu Tyr Asp Glu  
 2105 2110 2115  
 Leu Gly Ser Gly Ala Asp Ala Ser Ala Thr Gln Ala Ala Arg Ser  
 2120 2125 2130  
 Thr Asp Val Ala Ala Val Val Val Pro Ile Leu Phe Leu Ile Leu  
 2135 2140 2145  
 Leu Ser Leu Gly Val Gly Phe Ala Ile Leu Tyr Thr Lys His Arg  
 2150 2155 2160  
 Arg Leu Gln Ser Ser Phe Thr Ala Phe Ala Asn Ser His Tyr Ser  
 2165 2170 2175  
 Ser Arg Leu Gly Ser Ala Ile Phe Ser Ser Gly Asp Asp Leu Gly  
 2180 2185 2190



## Nonprovisional IP-017.ST25.txt

Glu Asp Asp Glu Asp Ala Pro Met Ile Thr Gly Phe Ser Asp Asp  
 2195 2200 2205

Val Pro Met Val Ile Ala  
 2210

<210> 90  
 <211> 862  
 <212> PRT  
 <213> MOUSE

<400> 90

Met Ser Thr Ala Asp Leu Met Arg Arg Trp Val Ile Ala Leu Leu Leu  
 1 5 10 15

Ala Ala Ala Gly Val Ala Ala Glu Asp Ser Cys Ser Arg Asn Glu Phe  
 20 25 30

Gln Cys Arg Asp Gly Lys Cys Ile Ala Ser Lys Trp Val Cys Asp Gly  
 35 40 45

Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Glu Thr Cys Met  
 50 55 60

Ser Val Thr Cys Gln Ser Asn Gln Phe Ser Cys Gly Gly Arg Val Ser  
 65 70 75 80

Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Gln Val Asp Cys Glu  
 85 90 95

Asn Asp Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp  
 100 105 110

Asp Phe Arg Cys Gln Asp Gly Lys Cys Ile Ser Pro Gln Phe Val Cys  
 115 120 125

Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Gln  
 130 135 140

Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Asn Ser Ser Ile Cys  
 145 150 155 160

Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly  
 165 170 175

Ser Asp Glu Trp Pro Gln Asn Cys Gln Gly Arg Asp Thr Ala Ser Lys  
 180 185 190

Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser  
 195 200 205

## Nonprovisional IP-017.ST25.txt

Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys  
 210 215 220  
 Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp  
 225 230 235 240  
 Glu Phe Gln Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Gln Cys  
 245 250 255  
 Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val  
 260 265 270  
 Asn Val Thr Gln Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly  
 275 280 285  
 Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Gln  
 290 295 300  
 Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu  
 305 310 315 320  
 Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly  
 325 330 335  
 Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg  
 340 345 350  
 Cys Glu Asp Ile Asp Glu Cys Gln Glu Pro Asp Thr Cys Ser Gln Leu  
 355 360 365  
 Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Gln Ala Gly Phe  
 370 375 380  
 His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Gly Ser Ile Gly  
 385 390 395 400  
 Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp  
 405 410 415  
 Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala  
 420 425 430  
 Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser  
 435 440 445  
 Gln Lys Lys Ile Tyr Ser Ala Leu Met Asp Gln Ala Pro Asn Leu Ser  
 450 455 460  
 Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala  
 465 470 475 480

## Nonprovisional IP-017.ST25.txt

Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly  
 485 490 495  
 Ser Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Arg Thr Leu Phe  
 500 505 510  
 Gln Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His  
 515 520 525  
 Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys  
 530 535 540  
 Gly Gly Leu Asn Gly Val Asp Ile His Ser Leu Val Thr Glu Asn Ile  
 545 550 555 560  
 Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Ser Ser Gly Arg Leu Tyr  
 565 570 575  
 Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly  
 580 585 590  
 Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro  
 595 600 605  
 Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile  
 610 615 620  
 Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn  
 625 630 635 640  
 Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His  
 645 650 655  
 Lys Val Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Thr Thr Ala Leu  
 660 665 670  
 Leu Pro Asn Ser Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile  
 675 680 685  
 Gly Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu  
 690 695 700  
 Leu Ala Glu Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu  
 705 710 715 720  
 Thr Thr Gln Gly Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala  
 725 730 735  
 Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro  
 740 745 750

## Nonprovisional IP-017.ST25.txt

Arg Gln Pro Val Asp Thr Pro Gly Leu Ser Thr Val Ala Ser Val Thr  
 755 760 765  
 Val Ser His Gln Val Gln Gly Asp Met Ala Gly Arg Gly Asn Glu Glu  
 770 775 780  
 Gln Pro His Gly Val Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu  
 785 790 795  
 Val Ala Leu Leu Val Leu Gly Ala Val Leu Leu Trp Arg Asn Trp Arg  
 805 810 815  
 Leu Lys Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys  
 820 825 830  
 Thr Thr Glu Asp Glu Leu His Ile Cys Arg Ser Gln Asp Gly Tyr Thr  
 835 840 845  
 Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala  
 850 855 860  
 <210> 91  
 <211> 862  
 <212> PRT  
 <213> MOUSE  
 <400> 91  
 Met Ser Thr Ala Asp Leu Met Arg Arg Trp Val Ile Ala Leu Leu Leu  
 1 5 10 15  
 Ala Ala Ala Gly Val Ala Ala Glu Asp Ser Cys Ser Arg Asn Glu Phe  
 20 25 30  
 Gln Cys Arg Asp Gly Lys Cys Ile Ala Ser Lys Trp Val Cys Asp Gly  
 35 40 45  
 Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Glu Thr Cys Met  
 50 55 60  
 Ser Val Thr Cys Gln Ser Asn Gln Phe Ser Cys Gly Gly Arg Val Ser  
 65 70 75 80  
 Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Gln Val Asp Cys Glu  
 85 90 95  
 Asn Asp Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp  
 100 105 110  
 Asp Phe Arg Cys Gln Asp Gly Lys Cys Ile Ser Pro Gln Phe Val Cys  
 115 120 125

## Nonprovisional IP-017.ST25.txt

Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Gln  
 130 135 140  
 Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Asn Ser Ser Ile Cys  
 145 150 155 160  
 Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly  
 165 170 175  
 Ser Asp Glu Trp Pro Gln Asn Cys Gln Gly Arg Asp Thr Ala Ser Lys  
 180 185 190  
 Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser  
 195 200 205  
 Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys  
 210 215 220  
 Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp  
 225 230 235 240  
 Glu Phe Gln Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Gln Cys  
 245 250 255  
 Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val  
 260 265 270  
 Asn Val Thr Gln Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly  
 275 280 285  
 Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Gln  
 290 295 300  
 Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu  
 305 310 315 320  
 Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly  
 325 330 335  
 Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg  
 340 345 350  
 Cys Glu Asp Ile Asp Glu Cys Gln Glu Pro Asp Thr Cys Ser Gln Leu  
 355 360 365  
 Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Gln Ala Gly Phe  
 370 375 380  
 His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Gly Ser Ile Gly  
 385 390 395 400

## Nonprovisional IP-017.ST25.txt

Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp  
 405 410 415  
 Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala  
 420 425 430  
 Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser  
 435 440 445  
 Gln Lys Lys Ile Tyr Ser Ala Leu Met Asp Gln Ala Pro Asn Leu Ser  
 450 455 460  
 Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala  
 465 470 475 480  
 Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly  
 485 490 495  
 Ser Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Arg Thr Leu Phe  
 500 505 510  
 Gln Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His  
 515 520 525  
 Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys  
 530 535 540  
 Gly Gly Leu Asn Gly Val Asp Ile His Ser Leu Val Thr Glu Asn Ile  
 545 550 555 560  
 Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Ser Ser Gly Arg Leu Tyr  
 565 570 575  
 Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly  
 580 585 590  
 Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro  
 595 600 605  
 Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile  
 610 615 620  
 Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn  
 625 630 635 640  
 Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His  
 645 650 655  
 Lys Val Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Thr Thr Ala Leu  
 660 665 670

Nonprovisional IP-017.ST25.txt

Leu Pro Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile  
 675 680 685

Gly Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu  
 690 695 700

Leu Ala Lys Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu  
 705 710 715 720

Thr Thr Gln Gly Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala  
 725 730 735

Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro  
 740 745 750

Arg Gln Pro Val Asp Thr Pro Gly Leu Ser Thr Val Ala Ser Val Thr  
 755 760 765

Val Ser His Gln Val Gln Gly Asp Met Ala Gly Arg Gly Asn Glu Glu  
 770 775 780

Gln Pro His Gly Met Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu  
 785 790 795 800

Val Ala Leu Leu Val Leu Gly Ala Val Leu Leu Trp Arg Asn Trp Arg  
 805 810 815

Leu Lys Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr Gln Lys  
 820 825 830

Thr Thr Glu Asp Glu Leu His Ile Cys Arg Ser Gln Asp Gly Tyr Thr  
 835 840 845

Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala  
 850 855 860

<210> 92  
 <211> 864  
 <212> PRT  
 <213> MOUSE

<400> 92

Met Ser Thr Ala Asp Leu Met Arg Arg Trp Val Ile Ala Leu Leu Leu  
 1 5 10 15

Ala Ala Ala Gly Val Ala Val Glu Asp Ser Gly Ser Arg Asn Glu Phe  
 20 25 30

Gln Cys Arg Asp Gly Lys Cys Ile Ala Ser Lys Trp Val Cys Asp Gly  
 35 40 45

Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Lys Thr Cys Met  
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Nonprovisional IP-017.ST25.txt

50

55

60

Ser Val Thr Cys Gln Ser Asn Gln Phe Ser Cys Gly Gly Arg Val Ser  
 65 70 75 80  
 Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Gln Val Asp Cys Glu  
 85 90 95  
 Asn Asp Ser Asp Glu Gln Gly Cys Pro Pro Lys Thr Cys Ser Gln Asp  
 100 105 110  
 Asp Phe Arg Cys Gln Asp Gly Lys Cys Ile Ser Pro Gln Phe Val Cys  
 115 120 125  
 Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Pro  
 130 135 140  
 Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Lys Ser Ser Ile Cys  
 145 150 155 160  
 Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly  
 165 170 175  
 Ser His Glu Trp Pro Gln Asn Cys Gln Ala Glu Asp Thr Ala Ser Lys  
 180 185 190  
 Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser  
 195 200 205  
 Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys  
 210 215 220  
 Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp  
 225 230 235 240  
 Glu Phe Gln Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Gln Cys  
 245 250 255  
 Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val  
 260 265 270  
 Asn Val Thr Gln Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly  
 275 280 285  
 Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Gln  
 290 295 300  
 Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu  
 305 310 315 320  
 Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly  
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325

330

335

Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg  
 340 345 350

Cys Glu Asp Ile Asp Glu Cys Gln Glu Pro Asp Thr Cys Ser Gln Leu  
 355 360 365

Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Gln Ala Gly Phe  
 370 375 380

His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Gly Ser Ile Gly  
 385 390 395 400

Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp  
 405 410 415

Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala  
 420 425 430

Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser  
 435 440 445

Gln Lys Lys Ile Tyr Ser Ala Leu Met Asp Gln Ala Pro Asn Leu Ser  
 450 455 460

Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala  
 465 470 475 480

Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly  
 485 490 495

Ser Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Arg Thr Leu Phe  
 500 505 510

Gln Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His  
 515 520 525

Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys  
 530 535 540

Gly Gly Leu Asn Gly Val Asp Ile His Ser Leu Val Thr Glu Asn Ile  
 545 550 555 560

Gln Trp Pro Asn Gly Ile Thr Leu Asp Leu Ser Ser Gly Arg Leu Tyr  
 565 570 575

Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly  
 580 585 590

Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro  
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Nonprovisional IP-017.ST25.txt

595

600

605

Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile  
 610 615 620  
 Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn  
 625 630 635 640  
 Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His  
 645 650 655  
 Lys Val Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Thr Thr Ala Leu  
 660 665 670  
 Leu Pro Asn Gly Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile  
 675 680 685  
 Gly Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu  
 690 695 700  
 Leu Ala Lys Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu  
 705 710 715 720  
 Thr Thr Gln Gly Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala  
 725 730 735  
 Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro  
 740 745 750  
 Arg Gln Pro Val Asp Thr Pro Gly Leu Ser Thr Val Ala Ser Val Thr  
 755 760 765  
 Val Ser His Gln Val Gln Gly Asp Met Ala Gly Arg Gly Asn Glu Glu  
 770 775 780  
 Gln Pro His Gly Met Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu  
 785 790 795 800  
 Val Ala Leu Leu Val Leu Gly Ala Val Leu Leu Trp Arg Asn Trp Arg  
 805 810 815  
 Leu Lys Asn Ile Thr Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr  
 820 825 830  
 Gln Lys Thr Thr Glu Asp Glu Leu His Ile Cys Arg Ser Gln Asp Gly  
 835 840 845  
 Tyr Thr Tyr Pro Ser Arg Gln Met Val Ser Leu Glu Asp Asp Val Ala  
 850 855 860

## Nonprovisional IP-017.ST25.txt

<211> 873  
 <212> PRT  
 <213> MOUSE

<400> 93

Met Gly Thr Ser Ala Arg Trp Ala Leu Trp Leu Leu Leu Ala Leu Cys  
 1 5 10 15  
 Trp Ala Pro Arg Asp Ser Gly Ala Thr Ala Ser Gly Lys Lys Ala Lys  
 20 25 30  
 Cys Asp Ser Ser Gln Phe Gln Cys Thr Asn Gly Arg Cys Ile Thr Leu  
 35 40 45  
 Leu Trp Lys Cys Asp Gly Asp Glu Asp Cys Ala Asp Gly Ser Asp Glu  
 50 55 60  
 Lys Asn Cys Val Lys Lys Thr Cys Ala Glu Ser Asp Phe Val Cys Lys  
 65 70 75 80  
 Asn Gly Gln Cys Val Pro Asn Arg Trp Gln Cys Asp Gly Asp Pro Asp  
 85 90 95  
 Cys Glu Asp Gly Ser Asp Glu Ser Pro Glu Gln Cys His Met Arg Thr  
 100 105 110  
 Cys Arg Ile Asn Glu Ile Ser Cys Gly Ala Arg Ser Thr Gln Cys Ile  
 115 120 125  
 Pro Val Ser Trp Arg Cys Asp Gly Glu Asn Asp Cys Asp Asn Gly Glu  
 130 135 140  
 Asp Glu Glu Asn Cys Gly Asn Ile Thr Cys Ser Ala Asp Glu Phe Thr  
 145 150 155 160  
 Cys Ser Ser Gly Arg Cys Val Ser Arg Asn Phe Val Cys Asn Gly Gln  
 165 170 175  
 Asp Asp Cys Asp Asp Gly Ser Asp Glu Leu Asp Cys Ala Pro Pro Thr  
 180 185 190  
 Cys Gly Ala His Glu Phe Gln Cys Ser Thr Ser Ser Cys Ile Pro Leu  
 195 200 205  
 Ser Trp Val Cys Asp Asp Asp Ala Asp Cys Ser Asp Gln Ser Asp Glu  
 210 215 220  
 Ser Leu Glu Gln Cys Gly Arg Gln Pro Val Ile His Thr Lys Cys Pro  
 225 230 235 240  
 Thr Ser Glu Ile Gln Cys Gly Ser Gly Glu Cys Ile His Lys Lys Trp  
 245 250 255

## Nonprovisional IP-017.ST25.txt

Arg Cys Asp Gly Asp Pro Asp Cys Lys Asp Gly Ser Asp Glu Val Asn  
 260 265 270  
 Cys Pro Ser Arg Thr Cys Arg Pro Asp Gln Phe Glu Cys Glu Asp Gly  
 275 280 285  
 Ser Cys Ile His Gly Ser Arg Gln Ser Asn Gly Ile Arg Asp Cys Val  
 290 295 300  
 Asp Gly Ser Asp Glu Val Asn Cys Lys Asn Val Asn Gln Cys Leu Gly  
 305 310 315  
 Pro Gly Lys Phe Lys Cys Arg Ser Gly Glu Cys Ile Asp Met Ser Lys  
 325 330 335  
 Val Cys Asp Gln Glu Gln Asp Cys Arg Asp Trp Ser Asp Glu Pro Leu  
 340 345 350  
 Lys Glu Cys His Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Ser  
 355 360 365  
 His Ile Cys Lys Asp Leu Val Ile Gly Tyr Glu Cys Asp Cys Ala Ala  
 370 375 380  
 Gly Phe Glu Leu Ile Asp Arg Lys Thr Cys Gly Asp Ile Asp Glu Cys  
 385 390 395 400  
 Gln Asn Pro Gly Ile Cys Ser Gln Ile Cys Ile Asn Leu Lys Gly Gly  
 405 410 415  
 Tyr Lys Cys Glu Cys Ser Arg Gly Tyr Gln Met Asp Leu Ala Thr Gly  
 420 425 430  
 Val Cys Lys Ala Val Gly Lys Glu Pro Ser Leu Ile Phe Thr Asn Arg  
 435 440 445  
 Arg Asp Ile Arg Lys Ile Gly Leu Glu Arg Lys Glu Tyr Ile Gln Leu  
 450 455 460  
 Val Glu Gln Leu Arg Asn Thr Val Ala Leu Asp Ala Asp Ile Ala Ala  
 465 470 475 480  
 Gln Lys Leu Phe Trp Ala Asp Leu Ser Gln Lys Ala Ile Phe Ser Ala  
 485 490 495  
 Ser Ile Asp Asp Lys Val Gly Arg His Phe Lys Met Ile Asp Asn Val  
 500 505 510  
 Tyr Asn Pro Ala Ala Ile Ala Val Asp Trp Val Tyr Lys Thr Ile Tyr  
 515 520 525

## Nonprovisional IP-017.ST25.txt

Trp Thr Asp Ala Ala Ser Lys Thr Ile Ser Val Ala Thr Leu Asp Gly  
 530 535 540  
 Ala Lys Arg Lys Phe Leu Phe Asn Ser Asp Leu Arg Glu Pro Ala Ser  
 545 550 555 560  
 Ile Ala Val Asp Pro Leu Ser Gly Phe Val Tyr Trp Ser Asp Trp Gly  
 565 570 575  
 Glu Pro Ala Lys Ile Glu Lys Ala Gly Met Asn Gly Phe Asp Arg Arg  
 580 585 590  
 Pro Leu Val Thr Glu Asp Ile Gln Trp Pro Asn Gly Ile Thr Leu Asp  
 595 600 605  
 Leu Val Lys Ser Arg Leu Tyr Trp Leu Asp Ser Lys Leu His Met Leu  
 610 615 620  
 Ser Ser Val Asp Leu Asn Gly Gln Asp Arg Arg Ile Val Leu Lys Ser  
 625 630 635 640  
 Leu Glu Phe Leu Ala His Pro Leu Ala Leu Thr Ile Phe Glu Asp Arg  
 645 650 655  
 Val Tyr Trp Ile Asp Gly Glu Asn Glu Ala Val Tyr Gly Ala Asn Lys  
 660 665 670  
 Phe Thr Gly Ser Glu Leu Ala Thr Leu Val Asn Asn Leu Asn Asp Ala  
 675 680 685  
 Gln Asp Ile Ile Val Tyr His Glu Leu Val Gln Pro Ser Gly Lys Asn  
 690 695 700  
 Trp Cys Glu Asp Asp Met Glu Asn Gly Gly Cys Glu Tyr Leu Cys Leu  
 705 710 715 720  
 Pro Ala Pro Gln Ile Asn Asp His Ser Pro Lys Tyr Thr Cys Ser Cys  
 725 730 735  
 Pro Asn Gly Tyr Asn Leu Glu Glu Asn Gly Arg Glu Cys Gln Ser Thr  
 740 745 750  
 Ser Thr Pro Val Thr Tyr Ser Glu Thr Lys Asp Ile Asn Thr Thr Asp  
 755 760 765  
 Ile Leu Arg Thr Ser Gly Leu Val Pro Gly Gly Ile Asn Val Thr Thr  
 770 775 780  
 Ala Val Ser Glu Val Ser Val Pro Pro Lys Gly Thr Ser Ala Ala Trp  
 785 790 795 800

## Nonprovisional IP-017.ST25.txt

Ala Ile Leu Pro Leu Leu Leu Val Met Ala Ala Val Gly Gly Tyr  
805 810 815

Leu Met Trp Arg Asn Trp Gln His Lys Asn Met Lys Ser Met Asn Phe  
820 825 830

Asp Asn Pro Val Tyr Leu Lys Thr Thr Glu Glu Asp Leu Ser Ile Asp  
835 840 845

Ile Gly Arg His Ser Ala Ser Val Gly His Thr Tyr Pro Ala Ile Ser  
850 855 860

Val Val Ser Thr Asp Asp Asp Leu Ala  
865 870

<210> 94  
<211> 1614  
<212> PRT  
<213> MOUSE

<400> 94

Met Glu Thr Ala Pro Thr Arg Ala Pro Pro Pro Pro Pro Pro Leu  
1 5 10 15

Leu Leu Leu Val Leu Tyr Cys Ser Leu Val Pro Ala Ala Ala Ser Pro  
20 25 30

Leu Leu Leu Phe Ala Asn Arg Arg Asp Val Arg Leu Val Asp Ala Gly  
35 40 45

Gly Val Lys Leu Glu Ser Thr Ile Val Ala Ser Gly Leu Glu Asp Ala  
50 55 60

Ala Ala Val Asp Phe Gln Phe Ser Lys Gly Ala Val Tyr Trp Thr Asp  
65 70 75 80

Val Ser Glu Glu Ala Ile Lys Gln Thr Tyr Leu Asn Gln Thr Gly Ala  
85 90 95

Ala Ala Gln Asn Ile Val Ile Ser Gly Leu Val Ser Pro Asp Gly Leu  
100 105 110

Ala Cys Asp Trp Val Gly Lys Lys Leu Tyr Trp Thr Asp Ser Glu Thr  
115 120 125

Asn Arg Ile Glu Val Ala Asn Leu Asn Gly Thr Ser Arg Lys Val Leu  
130 135 140

Phe Trp Gln Asp Leu Asp Gln Pro Arg Ala Ile Ala Leu Asp Pro Ala  
145 150 155 160

## Nonprovisional IP-017.ST25.txt

His Gly Tyr Met Tyr Trp Thr Asp Trp Gly Glu Ala Pro Arg Ile Glu  
 165 170 175  
 Arg Ala Gly Met Asp Gly Ser Thr Arg Lys Ile Ile Val Asp Ser Asp  
 180 185 190  
 Ile Tyr Trp Pro Asn Gly Leu Thr Ile Asp Leu Glu Glu Gln Lys Leu  
 195 200 205  
 Tyr Trp Ala Asp Ala Lys Leu Ser Phe Ile His Arg Ala Asn Leu Asp  
 210 215 220  
 Gly Ser Phe Arg Gln Lys Val Val Glu Gly Ser Leu Thr His Pro Phe  
 225 230 235 240  
 Ala Leu Thr Leu Ser Gly Asp Thr Leu Tyr Trp Thr Asp Trp Gln Thr  
 245 250 255  
 Arg Ser Ile His Ala Cys Asn Lys Trp Thr Gly Glu Gln Arg Lys Glu  
 260 265 270  
 Ile Leu Ser Ala Leu Tyr Ser Pro Met Asp Ile Gln Val Leu Ser Gln  
 275 280 285  
 Glu Arg Gln Pro Pro Phe His Thr Pro Cys Glu Glu Asp Asn Gly Gly  
 290 295 300  
 Cys Ser His Leu Cys Leu Leu Ser Pro Arg Glu Pro Phe Tyr Ser Cys  
 305 310 315 320  
 Ala Cys Pro Thr Gly Val Gln Leu Gln Asp Asn Gly Lys Thr Cys Lys  
 325 330 335  
 Thr Gly Ala Glu Glu Val Leu Leu Leu Ala Arg Arg Thr Asp Leu Arg  
 340 345 350  
 Arg Ile Ser Leu Asp Thr Pro Asp Phe Thr Asp Ile Val Leu Gln Val  
 355 360 365  
 Gly Asp Ile Arg His Ala Ile Ala Ile Asp Tyr Asp Pro Leu Glu Gly  
 370 375 380  
 Tyr Val Tyr Trp Thr Asp Asp Glu Val Arg Ala Ile Arg Arg Ala Tyr  
 385 390 395 400  
 Leu Asp Gly Ser Gly Ala Gln Thr Leu Val Asn Thr Glu Ile Asn Asp  
 405 410 415  
 Pro Asp Gly Ile Ala Val Asp Trp Val Ala Arg Asn Leu Tyr Trp Thr  
 420 425 430

## Nonprovisional IP-017.ST25.txt

Asp Thr Gly Thr Asp Arg Ile Glu Val Thr Arg Leu Asn Gly Thr Ser  
 435 440 445  
 Arg Lys Ile Leu Val Ser Glu Asp Leu Asp Glu Pro Arg Ala Ile Val  
 450 455 460  
 Leu His Pro Val Met Gly Leu Met Tyr Trp Thr Asp Trp Gly Glu Asn  
 465 470 475 480  
 Pro Lys Ile Glu Cys Ala Asn Leu Asp Gly Arg Asp Arg His Val Leu  
 485 490 495  
 Val Asn Thr Ser Leu Gly Trp Pro Asn Gly Leu Ala Leu Asp Leu Gln  
 500 505 510  
 Glu Gly Lys Leu Tyr Trp Gly Asp Ala Lys Thr Asp Lys Ile Glu Val  
 515 520 525  
 Ile Asn Ile Asp Gly Thr Lys Arg Lys Thr Leu Leu Glu Asp Lys Leu  
 530 535 540  
 Pro His Ile Phe Gly Phe Thr Leu Leu Gly Asp Phe Ile Tyr Trp Thr  
 545 550 555 560  
 Asp Trp Gln Arg Arg Ser Ile Glu Arg Val His Lys Val Lys Ala Ser  
 565 570 575  
 Arg Asp Val Ile Ile Asp Gln Leu Pro Asp Leu Met Gly Leu Lys Ala  
 580 585 590  
 Val Asn Val Ala Lys Val Val Gly Thr Asn Pro Cys Ala Asp Gly Asn  
 595 600 605  
 Gly Gly Cys Ser His Leu Cys Phe Phe Thr Pro Arg Ala Thr Lys Cys  
 610 615 620  
 Gly Cys Pro Ile Gly Leu Glu Leu Leu Ser Asp Met Lys Thr Cys Ile  
 625 630 635 640  
 Ile Pro Glu Ala Phe Leu Val Phe Thr Ser Arg Ala Thr Ile His Arg  
 645 650 655  
 Ile Ser Leu Glu Thr Asn Asn Asn Asp Val Ala Ile Pro Leu Thr Gly  
 660 665 670  
 Val Lys Glu Ala Ser Ala Leu Asp Phe Asp Val Ser Asn Asn His Ile  
 675 680 685  
 Tyr Trp Thr Asp Val Ser Leu Lys Thr Ile Ser Arg Ala Phe Met Asn  
 690 695 700



## Nonprovisional IP-017.ST25.txt

Gly Ser Ser Val Glu His Val Ile Glu Phe Gly Leu Asp Tyr Pro Glu  
 705 710 715 720  
 Gly Met Ala Val Asp Trp Met Gly Lys Asn Leu Tyr Trp Ala Asp Thr  
 725 730 735  
 Gly Thr Asn Arg Ile Glu Val Ala Arg Leu Asp Gly Gln Phe Arg Gln  
 740 745 750  
 Val Leu Val Trp Arg Asp Leu Asp Asn Pro Arg Ser Leu Ala Leu Asp  
 755 760 765  
 Pro Thr Lys Gly Tyr Ile Tyr Trp Thr Glu Trp Gly Gly Lys Pro Arg  
 770 775 780  
 Ile Val Arg Ala Phe Met Asp Gly Thr Asn Cys Met Thr Leu Val Asp  
 785 790 795 800  
 Lys Val Gly Arg Ala Asn Asp Leu Thr Ile Asp Tyr Ala Asp Gln Arg  
 805 810 815  
 Leu Tyr Trp Thr Asp Leu Asp Thr Asn Met Ile Glu Ser Ser Asn Met  
 820 825 830  
 Leu Gly Gln Glu Arg Met Val Ile Ala Asp Asp Leu Pro Tyr Pro Phe  
 835 840 845  
 Gly Leu Thr Gln Tyr Ser Asp Tyr Ile Tyr Trp Thr Asp Trp Asn Leu  
 850 855 860  
 His Ser Ile Glu Arg Ala Asp Lys Thr Ser Gly Arg Asn Arg Thr Leu  
 865 870 875 880  
 Ile Gln Gly His Leu Asp Phe Val Met Asp Ile Leu Val Phe His Ser  
 885 890 895  
 Ser Arg Gln Asp Gly Leu Asn Asp Cys Val His Ser Asn Gly Gln Cys  
 900 905 910  
 Gly Gln Leu Cys Leu Ala Ile Pro Gly Gly His Arg Cys Gly Cys Ala  
 915 920 925  
 Ser His Tyr Thr Leu Asp Pro Ser Ser Arg Asn Cys Ser Pro Pro Ser  
 930 935 940  
 Thr Phe Leu Leu Phe Ser Gln Lys Phe Ala Ile Ser Arg Met Ile Pro  
 945 950 955 960  
 Asp Asp Gln Leu Ser Pro Asp Leu Val Leu Pro Leu His Gly Leu Arg  
 965 970 975

## Nonprovisional IP-017.ST25.txt

Asn Val Lys Ala Ile Asn Tyr Asp Pro Leu Asp Lys Phe Ile Tyr Trp  
                   980                                  985                                  990

Val Asp Gly Arg Gln Asn Ile Lys Arg Ala Lys Asp Asp Gly Thr Gln  
                   995                                  1000                                  1005

Pro Ser Met Leu Thr Ser Pro Ser Gln Ser Leu Ser Pro Asp Arg  
           1010                                  1015                                  1020

Gln Pro His Asp Leu Ser Ile Asp Ile Tyr Ser Arg Thr Leu Phe  
           1025                                  1030                                  1035

Trp Thr Cys Glu Ala Thr Asn Thr Ile Asn Val His Arg Leu Asp  
           1040                                  1045                                  1050

Gly Asp Ala Met Gly Val Val Leu Arg Gly Asp Arg Asp Lys Pro  
           1055                                  1060                                  1065

Arg Ala Ile Ala Val Asn Ala Glu Arg Gly Tyr Met Tyr Phe Thr  
           1070                                  1075                                  1080

Asn Met Gln Asp His Ala Ala Lys Ile Glu Arg Ala Ser Leu Asp  
           1085                                  1090                                  1095

Gly Thr Glu Arg Glu Val Leu Phe Thr Thr Gly Leu Ile Arg Pro  
           1100                                  1105                                  1110

Val Ala Leu Val Val Asp Asn Ala Leu Gly Lys Leu Phe Trp Val  
           1115                                  1120                                  1125

Asp Ala Asp Leu Lys Arg Ile Glu Ser Cys Asp Leu Ser Gly Ala  
           1130                                  1135                                  1140

Asn Arg Leu Thr Leu Glu Asp Ala Asn Ile Val Gln Pro Val Gly  
           1145                                  1150                                  1155

Leu Thr Val Leu Gly Arg His Leu Tyr Trp Ile Asp Arg Gln Gln  
           1160                                  1165                                  1170

Gln Met Ile Glu Arg Val Glu Lys Thr Thr Gly Asp Lys Arg Thr  
           1175                                  1180                                  1185

Arg Val Gln Gly Arg Val Thr His Leu Thr Gly Ile His Ala Val  
           1190                                  1195                                  1200

Glu Glu Val Ser Leu Glu Glu Phe Ser Ala His Pro Cys Ala Arg  
           1205                                  1210                                  1215

Asp Asn Gly Gly Cys Ser His Ile Cys Ile Ala Lys Gly Asp Gly  
           1220                                  1225                                  1230

## Nonprovisional IP-017.ST25.txt

Thr	Pro 1235	Arg	Cys	Ser	Cys	Pro 1240	Val	His	Leu	Val	Leu 1245	Leu	Gln	Asn
Leu	Leu 1250	Thr	Cys	Gly	Glu	Pro 1255	Pro	Thr	Cys	Ser	Pro 1260	Asp	Gln	Phe
Ala	Cys 1265	Thr	Thr	Gly	Glu	Ile 1270	Asp	Cys	Ile	Pro	Gly 1275	Ala	Trp	Arg
Cys	Asp 1280	Gly	Phe	Pro	Glu	Cys 1285	Ala	Asp	Gln	Ser	Asp 1290	Glu	Glu	Gly
Cys	Pro 1295	Val	Cys	Ser	Ala	Ser 1300	Gln	Phe	Pro	Cys	Ala 1305	Arg	Gly	Gln
Cys	Val 1310	Asp	Leu	Arg	Leu	Arg 1315	Cys	Asp	Gly	Glu	Ala 1320	Asp	Cys	Gln
Asp	Arg 1325	Ser	Asp	Glu	Ala	Asn 1330	Cys	Asp	Ala	Val	Cys 1335	Leu	Pro	Asn
Gln	Phe 1340	Arg	Cys	Thr	Ser	Gly 1345	Gln	Cys	Val	Leu	Ile 1350	Lys	Gln	Gln
Cys	Asp 1355	Ser	Phe	Pro	Asp	Cys 1360	Ala	Asp	Gly	Ser	Asp 1365	Glu	Leu	Met
Cys	Glu 1370	Ile	Asn	Lys	Pro	Pro 1375	Ser	Asp	Asp	Ile	Pro 1380	Ala	His	Ser
Ser	Ala 1385	Ile	Gly	Pro	Val	Ile 1390	Gly	Ile	Ile	Leu	Ser 1395	Leu	Phe	Val
Met	Gly 1400	Gly	Val	Tyr	Phe	Val 1405	Cys	Gln	Arg	Val	Met 1410	Cys	Gln	Arg
Tyr	Thr 1415	Gly	Ala	Ser	Gly	Pro 1420	Phe	Pro	His	Glu	Tyr 1425	Val	Gly	Gly
Ala	Pro 1430	His	Val	Pro	Leu	Asn 1435	Phe	Ile	Ala	Pro	Gly 1440	Gly	Ser	Gln
His	Gly 1445	Pro	Phe	Pro	Gly	Ile 1450	Pro	Cys	Ser	Lys	Ser 1455	Val	Met	Ser
Ser	Met 1460	Ser	Leu	Val	Gly	Gly 1465	Arg	Gly	Ser	Val	Pro 1470	Leu	Tyr	Asp
Arg	Asn 1475	His	Val	Thr	Gly	Ala 1480	Ser	Ser	Ser	Ser	Ser 1485	Ser	Ser	Thr

## Nonprovisional IP-017.ST25.txt

Lys Ala Thr Leu Tyr Pro Pro Ile Leu Asn Pro Pro Pro Ser Pro  
1490 1495 1500

Ala Thr Asp Pro Ser Leu Tyr Asn Val Asp Val Phe Tyr Ser Ser  
1505 1510 1515

Gly Ser Pro Ala Thr Ala Arg Pro Tyr Arg Pro Tyr Val Ile Arg  
1520 1525 1530

Gly Met Ala Pro Pro Thr Thr Pro Cys Ser Thr Asp Val Cys Asp  
1535 1540 1545

Ser Asp Tyr Ser Thr Ser Arg Trp Lys Ser Ser Lys Tyr Tyr Leu  
1550 1555 1560

Asp Leu Asn Ser Asp Ser Asp Pro Tyr Pro Pro Pro Pro Thr Pro  
1565 1570 1575

His Ser Gln Tyr Leu Ser Ala Glu Asp Ser Cys Pro Pro Ser Pro  
1580 1585 1590

Gly Thr Glu Arg Ser Tyr Cys His Leu Phe Pro Pro Pro Pro Ser  
1595 1600 1605

Pro Cys Thr Asp Ser Ser  
1610

<210> 95  
<211> 837  
<212> PRT  
<213> HOMO SAPIENS

<400> 95

Gly Asp Arg Cys Glu Arg Asn Glu Phe Gln Cys Gln Asp Gly Lys Cys  
1 5 10 15

Ile Ser Tyr Lys Trp Val Cys Asp Gly Ser Ala Glu Cys Gln Asp Gly  
20 25 30

Ser Asp Glu Ser Gln Glu Thr Cys Leu Ser Val Thr Cys Lys Ser Gly  
35 40 45

Asp Phe Ser Cys Gly Gly Arg Val Asn Arg Cys Ile Pro Gln Phe Trp  
50 55 60

Arg Cys Asp Gly Gln Val Asp Cys Asp Asn Gly Ser Asp Glu Gln Gly  
65 70 75 80

Cys Pro Pro Lys Thr Cys Ser Gln Asp Glu Phe Arg Cys His Asp Gly  
85 90 95

## Nonprovisional IP-017.ST25.txt

Lys Cys Ile Ser Arg Gln Phe Val Cys Asp Ser Asp Arg Asp Cys Leu  
 100 105 110  
 Asp Gly Ser Asp Glu Ala Ser Cys Pro Val Leu Thr Cys Gly Pro Ala  
 115 120 125  
 Ser Phe Gln Cys Asn Ser Ser Thr Cys Ile Pro Gln Leu Trp Ala Cys  
 130 135 140  
 Asp Asn Asp Pro Asp Cys Glu Asp Gly Ser Asp Glu Trp Pro Gln Arg  
 145 150 155 160  
 Cys Arg Gly Leu Tyr Val Phe Gln Gly Asp Ser Ser Pro Cys Ser Ala  
 165 170 175  
 Phe Glu Phe His Cys Leu Ser Gly Glu Cys Ile His Ser Ser Trp Arg  
 180 185 190  
 Cys Asp Gly Gly Pro Asp Cys Lys Asp Lys Ser Asp Glu Glu Asn Cys  
 195 200 205  
 Ala Val Ala Thr Cys Arg Pro Asp Glu Phe Gln Cys Ser Asp Gly Asn  
 210 215 220  
 Cys Ile His Gly Ser Arg Gln Cys Asp Arg Glu Tyr Asp Cys Lys Asp  
 225 230 235 240  
 Met Ser Asp Glu Val Gly Cys Val Asn Val Thr Leu Cys Glu Gly Pro  
 245 250 255  
 Asn Lys Phe Lys Cys His Ser Gly Glu Cys Ile Thr Leu Asp Lys Val  
 260 265 270  
 Cys Asn Met Ala Arg Asp Cys Arg Asp Trp Ser Asp Glu Pro Ile Lys  
 275 280 285  
 Glu Cys Gly Thr Asn Glu Cys Leu Asp Asn Asn Gly Gly Cys Ser His  
 290 295 300  
 Val Cys Asn Asp Leu Lys Ile Gly Tyr Glu Cys Leu Cys Pro Asp Gly  
 305 310 315 320  
 Phe Gln Leu Val Ala Gln Arg Arg Cys Glu Asp Ile Asp Glu Cys Gln  
 325 330 335  
 Asp Pro Asp Thr Cys Ser Gln Leu Cys Val Asn Leu Glu Gly Gly Tyr  
 340 345 350  
 Lys Cys Gln Cys Glu Glu Gly Phe Gln Leu Asp Pro His Thr Lys Ala  
 355 360 365

Nonprovisional IP-017.ST25.txt

Cys Lys Ala Val Gly Ser Ile Ala Tyr Leu Phe Phe Thr Asn Arg His  
 370 375 380  
 Glu Val Arg Lys Met Thr Leu Asp Arg Ser Glu Tyr Thr Ser Leu Ile  
 385 390 395 400  
 Pro Asn Leu Arg Asn Val Val Ala Leu Asp Thr Glu Val Ala Ser Asn  
 405 410 415  
 Arg Ile Tyr Trp Ser Asp Leu Ser Gln Arg Met Ile Cys Ser Thr Gln  
 420 425 430  
 Leu Asp Arg Ala His Gly Val Ser Ser Tyr Asp Thr Val Ile Ser Arg  
 435 440 445  
 Asp Ile Gln Ala Pro Asp Gly Leu Ala Val Asp Trp Ile His Ser Asn  
 450 455 460  
 Ile Tyr Trp Thr Asp Ser Val Leu Gly Thr Val Ser Val Ala Asp Thr  
 465 470 475 480  
 Lys Gly Val Lys Arg Lys Thr Leu Phe Arg Glu Asn Gly Ser Lys Pro  
 485 490 495  
 Arg Ala Ile Val Val Asp Pro Val His Gly Phe Met Tyr Trp Thr Asp  
 500 505 510  
 Trp Gly Thr Pro Ala Lys Ile Lys Lys Gly Gly Leu Asn Gly Val Asp  
 515 520 525  
 Ile Tyr Ser Leu Val Thr Glu Asn Ile Gln Trp Pro Asn Gly Ile Thr  
 530 535 540  
 Leu Asp Leu Leu Ser Gly Arg Leu Tyr Trp Val Asp Ser Lys Leu His  
 545 550 555 560  
 Ser Ile Ser Ser Ile Asp Val Asn Gly Gly Asn Arg Lys Thr Ile Leu  
 565 570 575  
 Glu Asp Glu Lys Arg Leu Ala His Pro Phe Ser Leu Ala Val Phe Glu  
 580 585 590  
 Asp Lys Val Phe Trp Thr Asp Ile Ile Asn Glu Ala Ile Phe Ser Ala  
 595 600 605  
 Asn Arg Leu Thr Gly Ser Asp Val Asn Leu Leu Ala Glu Asn Leu Leu  
 610 615 620  
 Ser Pro Glu Asp Met Val Leu Phe His Asn Leu Thr Gln Pro Arg Gly  
 625 630 635 640

## Nonprovisional IP-017.ST25.txt

Val Asn Trp Cys Glu Arg Thr Thr Leu Ser Asn Gly Gly Cys Gln Tyr  
645 650 655

Leu Cys Leu Pro Ala Ser Gln Ile Asn Pro His Ser Pro Lys Phe Thr  
660 665 670

Cys Ala Cys Pro Asp Gly Met Leu Leu Ala Arg Asp Met Arg Ser Cys  
675 680 685

Leu Thr Glu Ala Glu Ala Ala Val Ala Thr Gln Glu Thr Ser Thr Val  
690 695 700

Arg Leu Lys Val Ser Ser Thr Ala Val Arg Thr Gln His Thr Thr Thr  
705 710 715 720

Arg Pro Val Pro Asp Thr Ser Arg Leu Pro Gly Ala Thr Pro Gly Leu  
725 730 735

Thr Thr Val Glu Ile Val Thr Met Ser His Gln Ala Leu Gly Asp Val  
740 745 750

Ala Gly Arg Gly Asn Glu Lys Lys Pro Ser Ser Val Arg Ala Leu Ser  
755 760 765

Ile Val Leu Pro Ile Val Leu Leu Val Phe Leu Cys Leu Gly Val Phe  
770 775 780

Leu Leu Trp Lys Asn Trp Arg Leu Lys Asn Ile Asn Ser Ile Asn Phe  
785 790 795 800

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## Nonprovisional IP-017.ST25.txt

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## Nonprovisional IP-017.ST25.txt

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Tyr Ser His Val Val Lys Pro Val Pro Ala His Pro Ser Ser Asn Ser  
 35 40 45

Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Asn Thr Gly  
 50 55 60

Leu Asp Arg Asn Thr Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser  
 65 70 75 80

Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Leu Lys  
 85 90 95

Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn  
 100 105 110

Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser  
 115 120 125

Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln  
 130 135 140

Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val  
 145 150 155 160

Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser  
 165 170 175

His Asn Phe Glu Ser Met Ser Pro Ala Lys Pro Val Gln His His Arg  
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Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Met Ser  
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## Nonprovisional IP-017.ST25.txt

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<400> 105

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Tyr Ser His Val Val Lys Pro Val Ser Ala His Pro Ser Ser Asn Ser  
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Thr Leu Asn Gln Ala Arg Asn Gly Gly Arg His Phe Ser Ser Thr Gly  
 50 55 60

Leu Asp Arg Asn Ser Arg Val Gln Val Gly Cys Arg Glu Leu Arg Ser  
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Thr Lys Tyr Ile Ser Asp Gly Gln Cys Thr Ser Ile Ser Pro Leu Lys  
 85 90 95

Glu Leu Val Cys Ala Gly Glu Cys Leu Pro Leu Pro Val Leu Pro Asn  
 100 105 110

Trp Ile Gly Gly Gly Tyr Gly Thr Lys Tyr Trp Ser Arg Arg Ser Ser  
 115 120 125

Gln Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln  
 130 135 140

Leu Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val  
 145 150 155 160

Thr Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser  
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His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg  
 180 185 190

Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser  
 195 200 205

<210> 106  
 <211> 126  
 <212> PRT  
 <213> DANIO RERIO

<400> 106

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 Page 327

Nonprovisional IP-017.ST25.txt

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 Pro Thr His Leu Leu Pro Asn Trp Ile Gly Gly Gly His Tyr Trp Ser  
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 Ile Thr Ala Val Thr Ser Cys Thr Cys Lys Arg Tyr Thr Arg Gln Asn  
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 Glu Leu Glu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly Arg  
                     50                      55                      60  
 Pro Pro His His Pro Phe Glu Thr Lys Asp Val Ser Glu Tyr Ser Cys  
 65                      70                      75                      80  
 Arg Glu Leu His Phe Thr Arg Tyr Val Thr Asp Gly Pro Cys Arg Ser  
                     85                      90                      95  
 Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly Pro Ala  
                     100                      105                      110  
 Arg Leu Leu Pro Asn Ala Ile Gly Arg Gly Lys Trp Trp Arg Pro Ser  
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## Nonprovisional IP-017.ST25.txt

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Leu Val Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln  
 165 170 175

Ser Glu Leu Lys Asp Phe Gly Pro Glu Ala Ala Arg Pro Gln Lys Gly  
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Leu Glu Asn Ala Tyr  
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<400> 109

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Leu Pro Glu Leu Asn Asn Lys Thr Met Asn Arg Ala Glu Asn Gly Gly  
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## Nonprovisional IP-017.ST25.txt

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## Nonprovisional IP-017.ST25.txt

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## Nonprovisional IP-017.ST25.txt

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Nonprovisional IP-017.ST25.txt

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## Nonprovisional IP-017.ST25.txt

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<213> RABBIT

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## Nonprovisional IP-017.ST25.txt

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 <211> 56  
 <212> PRT  
 <213> MOUSE

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 <222> (22)..(22)  
 <223> Xaa can be any naturally occurring amino acid

<220>  
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 <223> Xaa can be any naturally occurring amino acid

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Gly Cys Arg Glu Leu Arg Ser Thr Lys Tyr Ile Ser Asp Gly Gln Cys  
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Thr Ser Ile Ser Pro Xaa Lys Glu Leu Val Cys Ala Gly Glu Cys Leu  
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Pro Leu Pro Val Leu Pro Asn Trp Ile Gly Gly Gly Tyr Gly Thr Lys  
 35 40 45

Tyr Trp Ser Arg Arg Ser Xaa Gln  
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<210> 115  
 <211> 77  
 <212> PRT  
 <213> MOUSE

<400> 115

Glu Trp Arg Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln Leu  
 1 5 10 15

Gln Cys Gln Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val Thr  
 Page 335

Nonprovisional IP-017.ST25.txt

20

25

30

Ala Cys Lys Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser Ser His  
35 40 45

Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His Arg Glu  
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Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser  
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<210>	116
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<212>	PRT
<213>	MOUSE

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<223> Xaa can be any naturally occurring amino acid
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<400> 116

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1 5 10 15

Thr Ser Ile Ser Pro Xaa Lys Glu Leu Val Cys Ala Gly Glu Cys  
20 25 30

<210>	117
<211>	28
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Lys Tyr Trp Ser Arg Arg Ser Xaa Gln Glu Trp Arg  
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<211>	43
<212>	PRT
<213>	MOUSE

<400> 118

Cys Val Asn Asp Lys Thr Arg Thr Gln Arg Ile Gln Leu Gln Cys Gln  
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Nonprovisional IP-017.ST25.txt

Asp Gly Ser Thr Arg Thr Tyr Lys Ile Thr Val Val Thr Ala Cys Lys  
 20 25 30

Cys Lys Arg Tyr Thr Arg Gln His Asn Glu Ser  
 35 40

<210> 119  
 <211> 31  
 <212> PRT  
 <213> MOUSE

<400> 119

Ser His Asn Phe Glu Ser Val Ser Pro Ala Lys Pro Ala Gln His His  
 1 5 10 15

Arg Glu Arg Lys Arg Ala Ser Lys Ser Ser Lys His Ser Leu Ser  
 20 25 30

<210> 120  
 <211> 52  
 <212> PRT  
 <213> MOUSE

<400> 120

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Arg Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys Gly  
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 35 40 45

Pro Asn Gly Pro  
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<210> 121  
 <211> 83  
 <212> PRT  
 <213> MOUSE

<400> 121

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 20 25 30

Ala Ser Cys Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser Glu  
 35 40 45

Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg Lys  
 50 55 60

## Nonprovisional IP-017.ST25.txt

Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu Glu  
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Asn Ala Tyr

<210> 122  
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 <212> PRT  
 <213> MOUSE

<400> 122

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 1 5 10 15

Arg Ser Ala Lys Pro Val Thr Glu Leu Val Cys Ser Gly Gln Cys  
 20 25 30

<210> 123  
 <211> 24  
 <212> PRT  
 <213> MOUSE

<400> 123

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Arg Pro Asn Gly Pro Asp Phe Arg  
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 <211> 44  
 <212> PRT  
 <213> MOUSE

<400> 124

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Gly Gly Ala Ala Pro Arg Ser Arg Lys Val Arg Leu Val Ala Ser Cys  
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Lys Cys Lys Arg Leu Thr Arg Phe His Asn Gln Ser  
 35 40

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 <213> MOUSE

<400> 125

Glu Leu Lys Asp Phe Gly Pro Glu Thr Ala Arg Pro Gln Lys Gly Arg  
 1 5 10 15

## Nonprovisional IP-017.ST25.txt

Lys Pro Arg Pro Gly Ala Arg Gly Ala Lys Ala Asn Gln Ala Glu Leu  
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Glu Asn Ala Tyr  
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<213>	MOUSE

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<223> n is a, c, g, or t
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## Nonprovisional IP-017.ST25.txt

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 <223> n is a, c, g, or t

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<400> 129  
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<210> 130  
 <211> 20  
 <212> DNA  
 <213> XENOPUS

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 <223> n is a, c, g, or t

<220>  
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<220>  
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## Nonprovisional IP-017.ST25.txt

<400> 130  
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<210> 131  
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 <213> XENOPUS

<400> 131  
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<210> 132  
 <211> 25  
 <212> DNA  
 <213> XENOPUS

<400> 132  
 agcagtgaag ccttgagaca accat 25

<210> 133  
 <211> 1718  
 <212> DNA  
 <213> RAT

<400> 133  
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 gtgggttaaac ctgtttcagc acacccagc agcaacagca ccttgaatca agccaggaat 240  
 ggaggcaggc acttcagtag cacgggactg gatcgaaata gtcgagttca agtgggctgc 300  
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## Nonprovisional IP-017.ST25.txt

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tttccagtct cagtgtgaaa ttatccccct cgtgttgacc tctcttggag tggaatgcca 1260
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tacactttgt cattagcgtg gttccctgta aagctgaagt tatgtaatac tttattattt 1560
agtccatgaa atcagaaggc agcttgacct tcggtgccat cggtttcttt taataaacat 1620
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<210> 134
<211> 25
<212> DNA
<213> MOUSE

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<400> 134
cgtgcctcat ctgcctactt gtgca 25

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<210> 135
<211> 27
<212> DNA
<213> MOUSE

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<400> 135
gaagtccttg agctccgact ggttgtg 27

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<210> 136
<211> 26
<212> DNA
<213> MOUSE

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<400> 136
ttctggcgag tcgacaattc tattgg 26

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<210> 137
<211> 26
<212> DNA
<213> MOUSE

```

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<400> 137
aacctttatc gtcgacgagc aattgg 26

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<210> 138
<211> 44
<212> DNA
<213> MOUSE

```

```

<400> 138
gcttcagcag cacatatggc tgttgtttat aacaacgaag ggac 44

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<210> 139
<211> 45
<212> DNA

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## Nonprovisional IP-017.ST25.txt

&lt;213&gt; MOUSE

&lt;400&gt; 139

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45

&lt;210&gt; 140

&lt;211&gt; 35

&lt;212&gt; DNA

&lt;213&gt; MOUSE

&lt;400&gt; 140

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35